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CONTENTS FOR MAY, 1936

Original Communications

Department of Clinical Reports

Department of Reviews and Abstracts

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Original Communications

INTERMITTENT CLAUDICATION STUDIED BY A GRAPHIC METHOD*

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ALTHOUGH pain is the striking subjective phenomenon of intermittent claudication and the criterion by which the severity of the condition is usually judged, fatigue of the contracting muscles precedes it. The early loss of contractile power or amplitude of contraction in muscle deprived of adequate blood supply is an objective phenomenon which can be recorded graphically. The ergograph[1-3] has demonstrated the theoretical and practical value of such graphic records of muscular fatigue.

The contractions depend upon the volition of the patient, and the ergograph records are to that extent subjective. The human calf muscles can, however, be made to contract involuntarily by electrical stimulation. The apparatus to be described was designed by one of us (E.M.L.) for the purposes of (1) producing involuntary contractions of the calf muscles by faradic stimulation at set intervals and (2) recording the development of fatigue graphically under standard conditions of stimulus and load. In this preliminary account are presented studies on normal subjects and on patients with peripheral vascular disease. Illustrative records indicate the usefulness of the procedure in estimating objectively the degree of claudication and in recording graphically changes occurring in the course of treatment.

APPARATUS

The apparatus for recording the development of fatigue in the muscles of the leg during stimulation is shown in lateral view by Fig. 1*A* and in end view by 1*B*. The base (*A*) consists of a board 33 inches long and 12 inches wide, extending from a point approximately 8 inches above the knee to a point about 10 inches below the sole of the foot. A vertical footboard (*B*), measuring 11.5 inches by 10 inches, is attached to this base by means of a hinge (*C*) constructed with its center of rotation approximately opposite to that of the ankle joint so that the foot may be

*From the Peripheral Vascular Section of the Robinette Foundation, Hospital of the University of Pennsylvania.

extended on the leg normally without undue strain. This footboard bears in the center a support for the heel (*D*) and two adjustable straps, one (*E*) passing over the ankle joint, the other (*F*) holding the instep lightly just proximal to the toes.

The footboard is held vertically against an adjustable stop (*G*) by two spiral springs (*H*) and several layers of sponge rubber (*I*) compressed slightly in the space between the lower edge of the footboard and the horizontal base. The force required to displace the footboard forward can be increased (a) by stretching one or both spiral springs more tightly on hooks (*J*) attached to each side of the base, or (b) by increasing the amount of sponge rubber under the edge of the footboard. In general it was found convenient to use six thicknesses of ¼ inch sponge rubber bandage with the springs only slightly stretched, i.e., in the first hook as shown in Fig. 1*A*. This tension resists contraction adequately and serves to bring the foot promptly back to the original vertical position as soon as muscular relaxation permits.

The calf muscles are stimulated through adjustable electrodes (*K*) applied one on each side of the leg in the position shown in Fig. 1*A*. Each electrode, measuring *in toto* 4 inches by 2½ inches with a thickness of ¾ inch, encloses a sheet of 1/16 inch lead soldered firmly to the upright (*L*). Since the muscles of the calf change their contour conspicuously during contraction, the inner surface of each electrode must be highly resilient in order to maintain contact with the skin uninterruptedly. Hence a layer of ¼ inch sponge rubber bandage was placed inside each lead plate and held in position by a series of flexible lead strips, 1/32 inch thick and ¼ inch wide, placed closely side by side to cover the entire inner surface of the sponge rubber. The ends of these strips were bent round the ends of the heavy lead plates and soldered to the outer surface of the plates, the whole electrode being enclosed in a gauze envelope. The sponge rubber, while forcing the gauze and each thin lead strip individually against the skin, still does not interfere with conduction of current. Each electrode is insulated by means of hard rubber from the holder (*M*) and is connected to the stimulating device described below by a separate wire (*N*). In preparing for an observation, the two electrodes are bent to conform to the shape of the calf muscles, soaked thoroughly in 80 per cent alcohol, and then fixed in place. Two thumbscrews (*O*) on the holder (*M*) are tightened so that the electrodes are held constantly and firmly against the skin.

A vertical iron rod (*P*) beyond the footboard supports a telechron motor (*Q*) which, through appropriate gears, propels a strip of adding machine paper (*R*) at the rate of 2 millimeters per second over a small drum (*S*) and, in addition, controls the duration and frequency of the electrical stimuli applied to the muscles of the leg through the electrode described above.

The rate of stimulation is controlled by the rotation of a notched bakelite disk (*T*) which keeps open the switch (*U*) except when one of the notches passes over the roller (*V*). The bakelite disk makes a complete rotation in four seconds. The disk shown in Fig. 1*B* contains four notches, and stimuli are therefore applied to the leg muscles once per second. Another disk containing two notches is used for stimulating every two seconds, and a third disk with one notch for stimulating every four seconds. The duration of each stimulus can be adjusted by a small vertical screw between the vacuum switch (*U*) and the roller (*V*). In these studies a stimulus of 0.07 second duration was used.

The vacuum switch (*U*) is connected in series with the secondary of an induction coil and with a manually operated switch which is used to interrupt the stimulating current completely during rest periods or when readjustments of the intensity of stimulation are necessary.

Since a tetanic contraction of short duration is desired, a faradic current from the secondary of an induction coil is used. Various types of mechanical induction apparatus and various rates of faradization were tried. It was found finally that

single phase 60 cycle, 110 volt alternating current in the primary circuit provided constant and effective stimuli. The intensity of contraction is varied by changing the amperage in the primary circuit. Appropriate resistances (e.g., a bank of lamps in parallel) are used to increase the amperage by 0.1 steps from 0.5 to 5.0

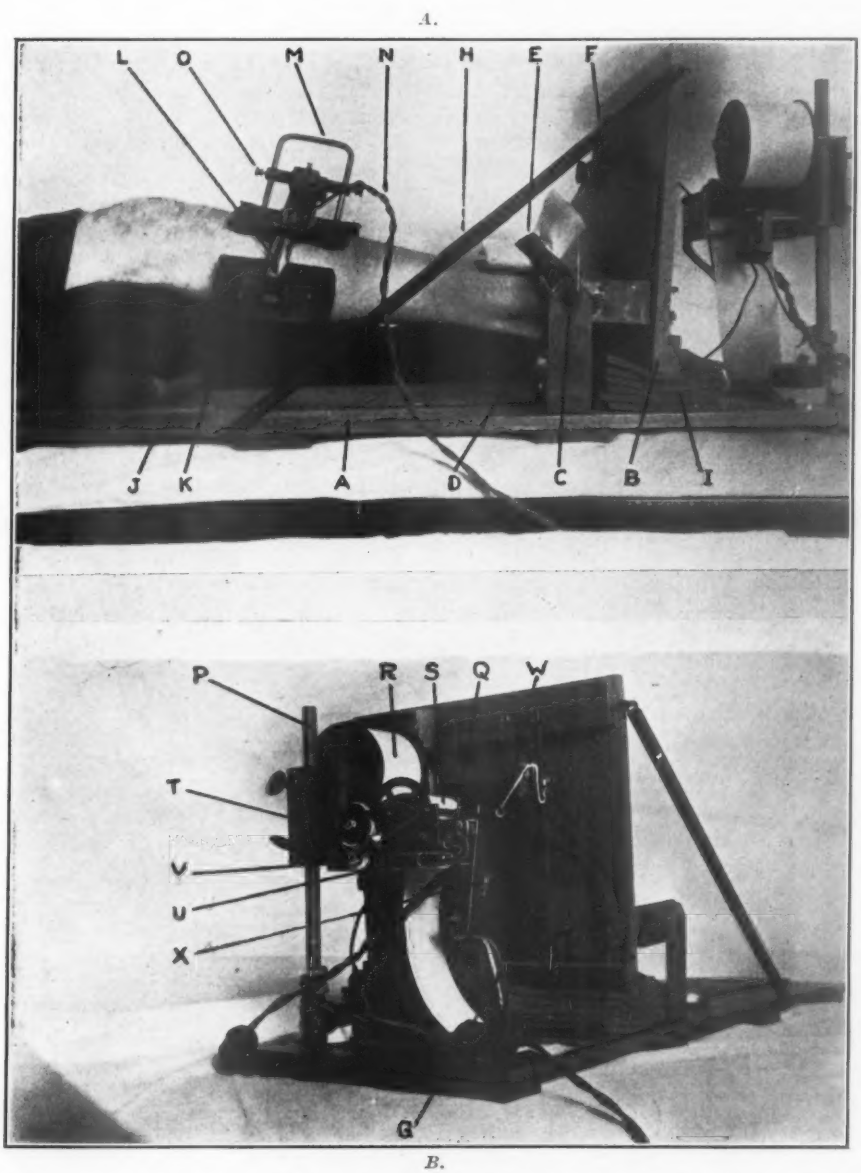

Fig. 1.—*A*, side and *B*, end-oblique views of apparatus for recording fatigue of calf muscles. For description see text.

amperes, the exact amount being read on an ammeter in series with the primary of the induction coil. One important precaution is to be observed carefully. The manual switch in the secondary circuit is *always turned off* before the amperage of

the primary circuit is changed, since otherwise the induced current temporarily stimulates undesirably painful and intense tetanus of the calf muscles.

During stimulation, contraction of the calf muscles extends the foot and the sole is pressed against the footboard. A metal rod (*W*) transmits any movement of the footboard to an ink writing pen (hidden behind the switch in Fig. 1*B*) mounted on a lever (*X*) held against the paper by a light spring. The excursion recorded by the pen is approximately equal to the excursion of the ball of the foot. The relation between excursion and the work performed against the resistance of steel springs and sponge rubber arranged as in Fig. 1 is as follows:

EXCURSION IN MILLIMETERS	WORK IN FOOT POUNDS*
4.0	0.69
10.0	2.50
20.0	6.40
30.0	13.65

*We are indebted to Mr. A. Rawson, of the Johnson Foundation, University of Pennsylvania Hospital, for this determination.

METHODS

The subject, after resting at least fifteen minutes, assumes a semi-reclining position on an examining table with a back support at an angle of 45 degrees. The foot is strapped in the holder, and the electrodes are placed as shown in Fig. 1. Stimuli are applied to the calf muscles at the rate of one in four seconds and the amperage, initially 0.5, is increased gradually until the amplitude of contraction recorded by the pen is between 18 and 25 mm.

The procedure adopted as routine was arranged to reveal (a) the effects of varying rates of stimulation, (b) the rate of recovery after different grades of fatigue had been produced, and (c) the cumulative effects of frequently repeated mild fatigue. The routine test required eighteen minutes for each leg and was arranged as follows:

1. Stimulation, once per four seconds, for two minutes.
2. Rest, one minute.
3. Stimulation, once per two seconds, for two minutes.
4. Rest, one minute.
5. Stimulation, once per second, for two minutes.
6. Rest, three minutes (renew alcohol on electrodes).
7. Stimulation, once per second, for one minute.
8. Rest, thirty seconds.
9. Etc., repeating parts 7 and 8 for a total of five short contraction and rest periods.

The long strip of graphic record can be cut into convenient lengths and mounted for easier analysis and filing.

OBSERVATIONS

A. Normal Subjects

A complete original record obtained from a normal subject is shown in Fig. 2. The amplitude of contraction did not diminish significantly until stimuli entered at the rate of one per second. The subject did not,

in the course of the test, experience fatigue or pain, though objective evidence of slightly reduced muscular efficiency was present.

The fatigue record obtained from a normal subject after blood flow in the extremity was stopped completely is shown in Fig. 3. A wide pneumatic cuff, encircling the thigh just above the knee, was inflated suddenly to 200 mm. of mercury just before beginning the usual routine

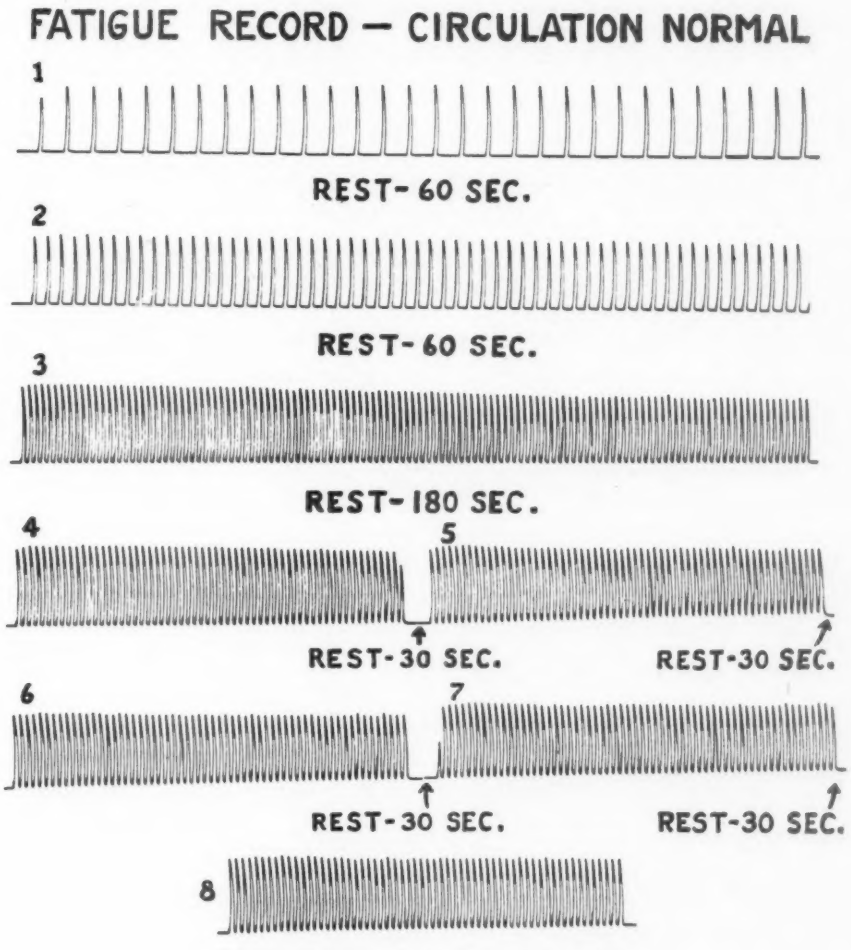

Fig. 2.—Fatigue record of normal subject.

stimulation (marked by arrow on record 1, upper part Fig. 3). The amplitude of contraction diminished measurably in the latter part of the first period though contractions were induced only once in four seconds. There was no recovery during the succeeding rest period. A few contractions at the rate of one in two seconds produced pain which increased steadily. The amplitude of contraction diminished conspicuously, and the reactions of the calf muscles became extremely sluggish,

both in contraction and in relaxation. The subsequent rest period again brought no recovery, and a few contractions at the rate of one per second developed intolerable pain. The cuff was released; during continued stimulation pain disappeared within twenty seconds and the

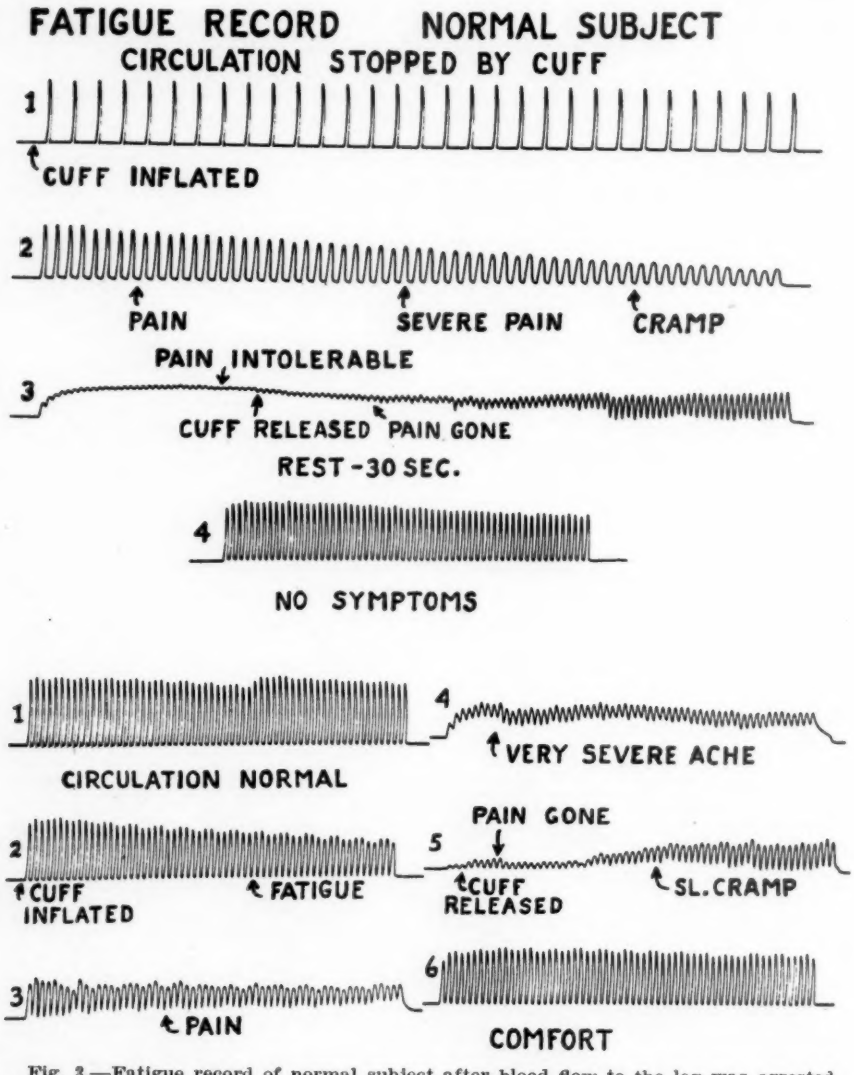

Fig. 3.—Fatigue record of normal subject after blood flow to the leg was arrested. Upper section (4 records) to be compared with records 1 to 4 inclusive, of Fig. 2. Lower section (6 records) to be compared with records 4 to 8, inclusive, of Fig. 2.

amplitude of contraction steadily increased. More complete recovery is shown in record 4 (upper part of Fig. 3), after the usual rest period. The lower section of Fig. 3, for comparison with lower Fig. 2, shows the effect of arresting blood flow on a series of contractions at the rate of one per second for periods of one minute with rest intervals of thirty

seconds. Again amplitude diminished considerably before pain appeared; contraction and relaxation became sluggish; and the rest periods did not produce the recovery observed when blood flow was free.

1. *Routine Fatigue Curves of Normal Subjects.*—The original records in Figs. 2 and 3 illustrate the changes produced when blood flow to the limb is completely obstructed, a condition far more severe than that to be expected in patients with intermittent claudication. To expedite plotting of results and more precise quantitative comparison, "fatigue curves" were prepared from the original records (Fig. 4).

The average height of the first five and last five strokes of each stimulation period were measured in millimeters. These amplitudes (in milli-

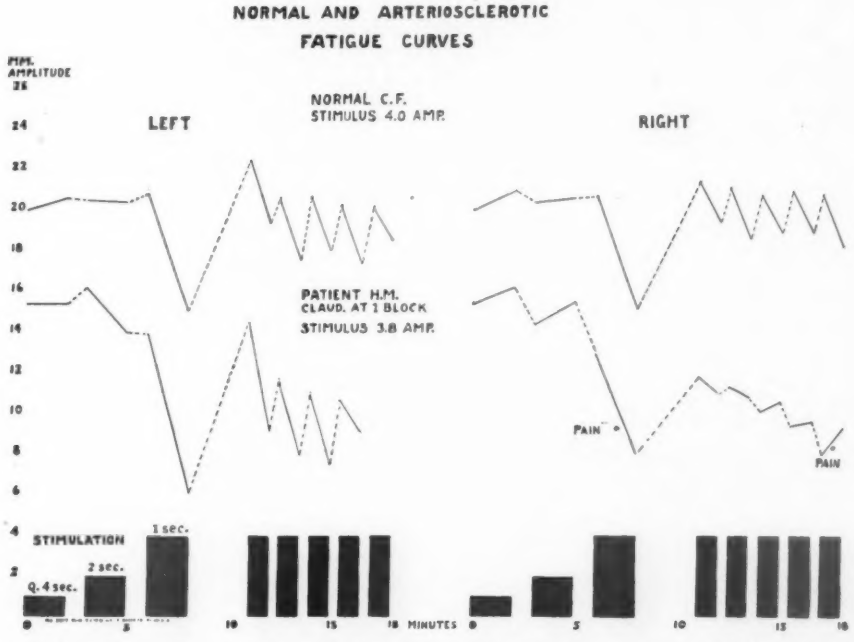

Fig. 4.—Examples of the contrasting curves obtained in a normal subject and a patient with intermittent claudication in the right leg. The amplitude of contraction at the beginning and end of each stimulus period has been plotted as described in the text. The gain or loss of amplitude during stimulation is indicated by the solid lines; the rest period by broken lines. The shaded areas below indicate the stimulation.

meters) plotted as abscissae against time in minutes as ordinates summarized the significant changes occurring during the entire test. In Fig. 4 the upper lines show such fatigue curves for a normal subject; the lower lines show, for contrast, the fatigue curves of a patient with claudication in the right leg. The solid portions of each curve represent stimulation periods; the shaded areas below indicate the rate of stimulation. The dotted portions of each curve represent rest periods.

The upper (normal) fatigue curve in Fig. 4 indicates that a current of 4.0 amperes produced a contraction amplitude of 20 mm. This initial

amplitude was maintained quantitatively throughout the test. Temporary fatigue, shown by diminished amplitude in the latter part of the contraction periods, disappeared completely in the brief rest periods.

Such complete fatigue curves were obtained in thirteen normal subjects, eleven males and two females, aged from nineteen to sixty-five years, with an average age of 35.6 years. Figure 5 gives the composite results for this group. To facilitate comparison, the average amplitude of the first fifteen contractions (performed at the rate of one in four seconds and, therefore, before fatigue sets in) was taken as 100 per cent. Subsequent amplitudes measured in the five strokes at the beginning and

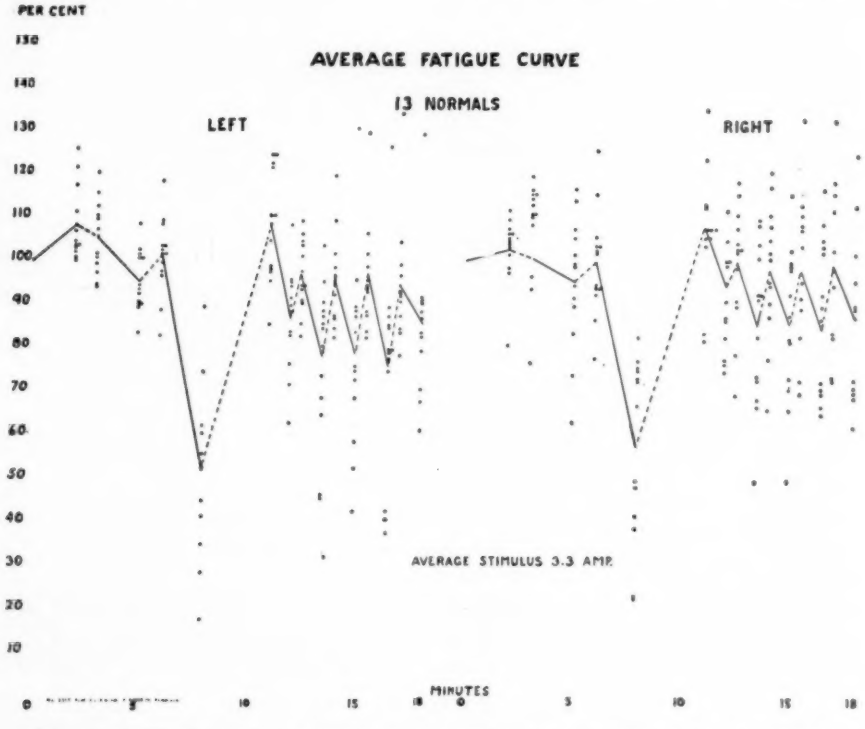

Fig. 5.—Composite curves plotted from the tracings of a series of normal subjects. The average amplitude of the first 15 excursions before fatigue sets in is used as 100 per cent. Solid lines, stimulation; dotted lines, rest periods. Timing and frequency of stimulation as in Fig. 4.

end of each stimulation period were expressed as a percentage of the original amplitude and charted as dots. Results thus summarized can be compared more easily with those obtained in patients with peripheral vascular disease. The observations on this normal group may be summarized briefly as follows:

1. Claudication pain did not appear at any time during the test, even after the two-minute period of rapid stimulation during which amplitude of contraction may decrease by 50 per cent. Mild fatigue in the foot or leg appeared in some instances.

2. During slow stimulation amplitude remained constant. Rapid stimulation gradually diminished the amplitude of contraction by 50 and 20 per cent in the two- and one-minute periods, respectively.

3. Whatever fatigue developed during periods of contraction disappeared during the stipulated rest periods, the amplitude of contraction returning almost completely to the initial amplitude after each brief rest.

4. Age, per se, did not affect the record. In this normal group those of sixty years or over produced curves similar to those of younger individuals.

5. General weakness after long confinement to bed produced for a given strength of stimulus, lower amplitudes and mild sensations of fatigue, but neither the claudication pain nor the rapid drop in amplitude which is characteristic of vascular disease.

2. *Fatigue Curves of Normal Subjects Under Experimental Conditions.*—*Complete obstruction of blood flow* (Fig. 3) produced fatigue or pain with loss of 7 per cent in amplitude even during slow stimulation (once in four seconds). In the succeeding rest period, there was no recovery. Stimulation at the rate of once in two seconds produced severe symptoms, and amplitude was reduced by 67 per cent of the initial value—again without recovery in the succeeding rest period. Intolerable pain developed after a few barely measurable contractions at the rate of once per second, and it was impossible to continue the test. Symptoms and signs of muscular fatigue disappeared shortly after blood flow was resumed.

Venous congestion by a pneumatic cuff inflated to a pressure of 40 to 60 mm. of mercury favored slightly the development of fatigue as measured subjectively and objectively. The changes were barely measurable and far less than those observed with completely obstructed blood flow. With cuff pressures of 80 to 120 mm. of mercury the amplitude of contraction was diminished as much as 60 per cent in the standard stimulation period. Two subjects suffered discomfort and one severe pain. The effects of marked venous congestion were roughly similar to those of mild peripheral vascular disease in patients.

Peripheral vasodilatation in normal individuals produced little or no change in the fatigue curve. Peripheral vasoconstriction was induced in normal subjects by exposure to an environmental temperature of 20-21° C. When digital temperatures reached 23° C., complete tracings were made. Vasodilatation was then induced by enclosing the forearms in electric heating pads and the body in blankets until skin temperature of the lower extremities rose above 30.5° C. Fatigue curves taken in this period showed rather less diminution in amplitude with exercise, but the changes observed were no greater than those that might be accounted for by a rest period of equal duration.

B. Fatigue Curves of Patients With Peripheral Vascular Disease

In twenty patients, seventeen men and three women, whose ages ranged between forty and seventy years (average fifty-one), the fatigue curves varied with the severity of the arterial deficiency. All differed from the curves obtained from normal subjects under comparable external conditions. These patients had intermittent claudication: fourteen because of arteriosclerosis, five because of thrombo-angiitis obliterans, while one fell in the group in which clinical differentiation between these two conditions is impossible.

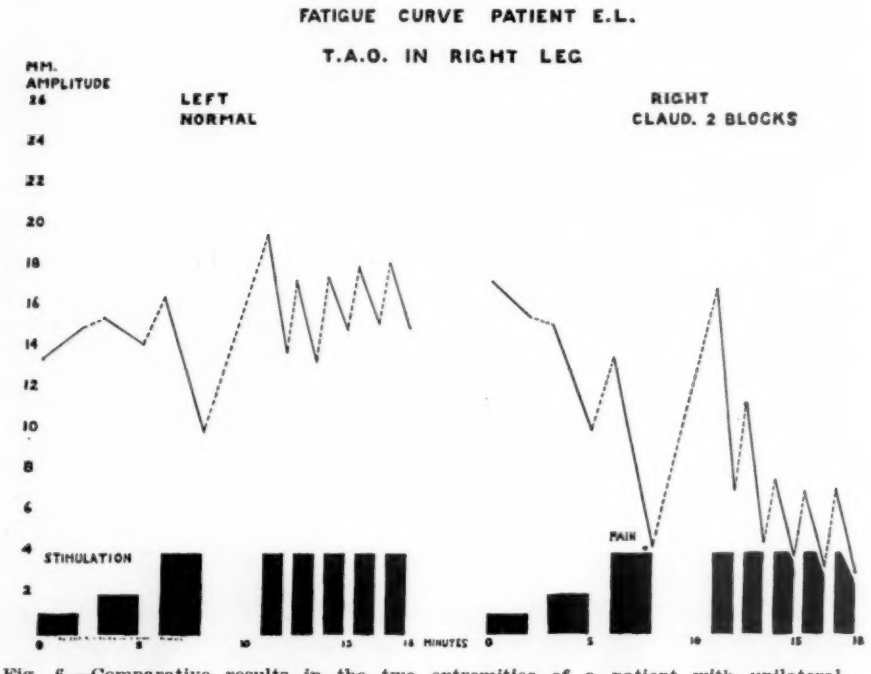

Fig. 6.—Comparative results in the two extremities of a patient with unilateral peripheral vascular disease.

The fatigue curves of a patient with arteriosclerosis are shown in Fig. 4 for comparison with the usual normal curve. This patient had claudication in the right leg only, but the responses of both legs were abnormal. A current of 3.8 amperes produced a contraction amplitude of 15 mm. This initial amplitude was not maintained owing to cumulative fatigue in the contraction period (solid lines) and cumulative incomplete recovery (dotted lines) during the rest periods. The objective changes were quantitatively greater in the leg presenting clinical evidence of ischemia.

A completely normal curve in one extremity may be associated with conspicuously reduced functional power in the other extremity, as shown in Fig. 6, which presents the fatigue curves of a patient with thrombo-

angiitis obliterans. Symptoms, including claudication upon walking two blocks, were limited to the right leg, as was also objective evidence of vascular deficiency.

The composite fatigue curves of twenty patients with peripheral vascular disease are shown in Fig. 7. The results on the more involved leg of each patient have been grouped together for comparison with the composite fatigue curves of normal subjects. As compared with the normal, records taken in patients with peripheral vascular disease present singly and collectively the following features:

1. The same intensity of stimulation (in amperes) generally produces a lower amplitude of contraction than in the normal subject. So far as

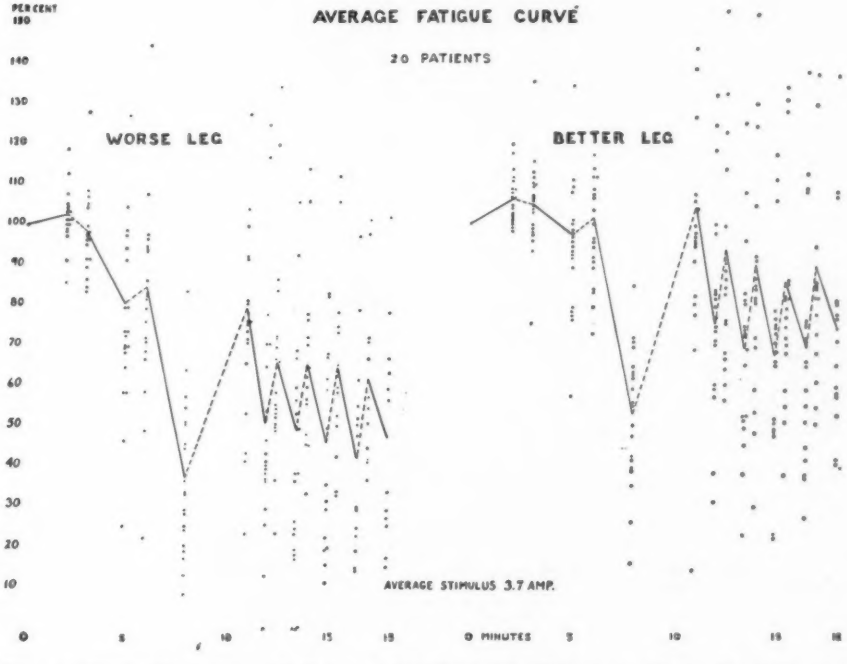

Fig. 7.—Composite curves plotted as described for Fig. 5 to show the lack of recovery of muscle power in patients with arterial disease.

can be judged at present, this difference cannot be attributed either to general weakness or to the smaller calf muscles usually found in patients with peripheral vascular disease.

2. The amplitude of contraction begins to diminish earlier and declines more rapidly in the course of the standard series of contractions.

3. In the routine rest periods muscle power recovers decidedly less completely so that the fatigue curves show, as a whole, a more or less conspicuous slope downward as the test proceeds.

4. This diminution in amplitude is associated with sensations of fatigue and claudication pain. The latter may be so severe that the test cannot be completed. When vascular occlusion has occurred recently,

the severity of fatigue and pain resembles very closely that observed in normal subjects whose blood flow to the calf muscles is completely interrupted by a pneumatic cuff.

C. Fatigue Curves of Patients With Peripheral Vascular Disease in the Course of Treatment

As clinical improvement occurs in the course of therapy, pathological fatigue curves should gradually return toward the normal form if that improvement is due to restoration of circulation. Two charts (Figs. 8 and 9) are included to indicate the possible clinical usefulness of the procedure in this regard.

Figure 8 shows two fatigue curves made in the course of recovery after sudden deprivation of major blood supply by thrombosis. In the earlier test it was impossible to complete the procedure owing to the development of severe pain associated with complete loss of contractile

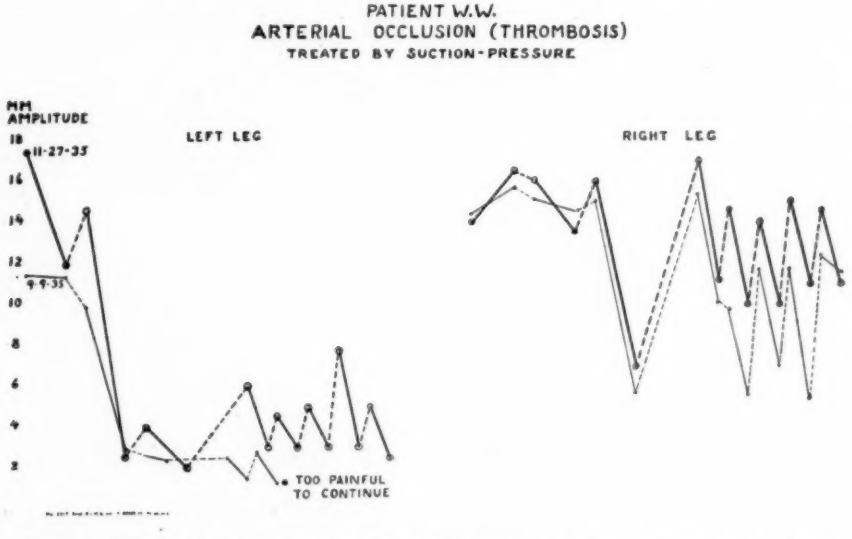

Fig. 8.—Effect of bed rest and thirty-seven hours of suction pressure to left leg in acute ischemia of the extremity. Light lines, curve before treatment; heavy lines, after clinical improvement was definite.

power. Later, contractile power was still conspicuously reduced, but the recovery during each rest period was much increased, and the test could be completed without pain. In the interim the patient had been treated by bed rest and thirty-seven hours of suction and pressure therapy for the left leg. Figure 9 exemplifies a series of curves being assembled in a study of the effects of tissue extract injections on intermittent claudication. Between the two tests shown, the patient received a total of twenty injections in a period of ten weeks with gratifying relief of claudication. A short period of suction and pressure therapy had produced only very slight benefit.

DISCUSSION

The manifestations of intermittent claudication are often entirely subjective and, like the angina of effort, they are open to misinterpretation by the patient or his physician. An objective test of circulation in the calf muscles is most needed when claudication is suspected in a patient in or near the arteriosclerotic age who still retains normal foot color, vasodilator responses, peripheral pulses, and roentgenogram. Moreover, pain in the lower extremities brought on by activity may be due to faulty mechanism of an orthopedic type, to neurological disorders, to anemia or to neurosis. It is in these patients that an objective test is valuable for diagnostic purposes. When the history of intermittent claudication is completely typical and when obvious evidence of arterio-

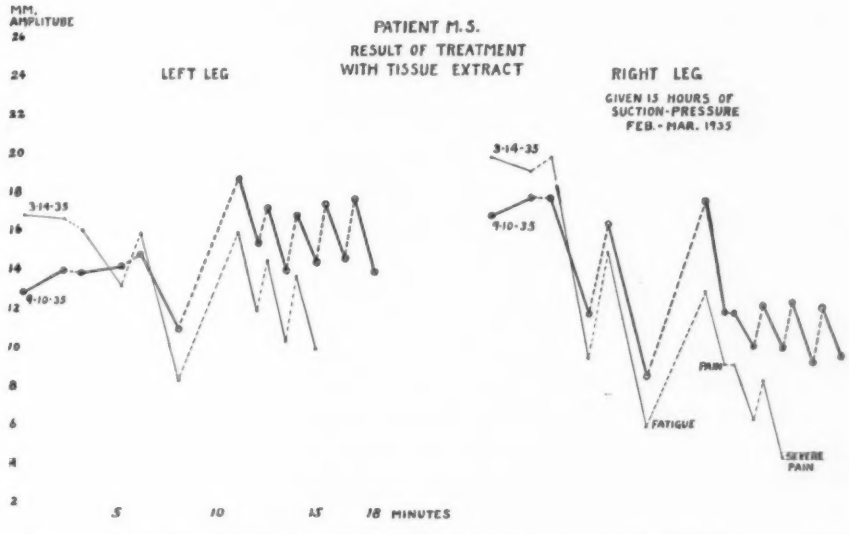

Fig. 9.—Example of graphic record of improvement with treatment in a case of arteriosclerosis. Twenty injections of tissue extract were given between the dates indicated.

sclerosis or other arterial disease is present, refined objective tests are not necessary for proper diagnosis.

During treatment, the effectiveness of therapy is usually estimated from the patient's own observations during uncontrolled exercise or during standard pacing such as described by Barker, Brown, and Roth.[4] The apparatus and the method presented above permit the production and objective recording of the fatigue of intermittent claudication, which so far has been described for the most part in terms of subjective sensation. It should be possible to observe more accurately than heretofore the effects of peripheral vascular disease on the function of the calf muscles, as well as the effects of therapy. It must be remembered, however, that muscle weakness or atrophy due to other than vascular causes,

may also produce abnormal curves. History, routine examination, and the form of the tracing should prevent difficulties in differential diagnosis.

The passage of faradic current through the skin produces a peculiar sensation best described, perhaps, by the terms "tingling" or "thrill." Under proper conditions there should be little or no pain. Of the fifty patients of all types so far tested only one, a highly neurotic woman, experienced such discomfort at the electrodes that the test had to be discontinued. A certain amount of cooperation on the part of the patient is necessary for obtaining good records; the muscles must be relaxed, not voluntarily contracted owing to tension or apprehension. In excitable individuals reassurance and slow increase of amperage will favor complete relaxation.

The electrodes should not be placed too near the peroneal or anterior tibial group of muscles. If the calf muscles and their antagonists are both stimulated, fatigue occurs earlier than would otherwise be the case owing to the double load against which the calf muscles must contract. Though somewhat time-consuming the test is relatively simple and can be carried out completely by a trained technician. The objective character of the results and their graphic recording compensate for the additional time and effort involved.

SUMMARY

A method of recording graphically the fatigue of the muscles involved in intermittent claudication is described. The calf muscles are stimulated faradically at selected rates for brief periods, without depending upon the volition of the subject. Fixed periods of stimulation, alternating with short rest periods, allow the measuring under standard conditions not only of the rate of fatigue, but also of the rate of recovery.

A series of normal fatigue curves is compared with a series of curves obtained from patients with peripheral vascular disease. Certain typical changes are related to deficient arterial blood supply.

It is suggested that the method may aid in detecting vascular insufficiency involving the calf muscles in questionable cases and that it may assist in estimating objectively the efficacy of therapeutic measures.

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THE INEFFECTIVENESS OF DRUGS UPON COLLATERAL FLOW AFTER EXPERIMENTAL CORONARY OCCLUSION IN DOGS*†

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OPINION is still at variance as to the completeness of the ischemia which follows total occlusion of a large coronary branch and as to the chances of promptly starting sufficient collateral blood flow by use of drugs to prevent contractile failure or to minimize the succeeding necrosis and fibrosis. A complete answer cannot be expected from experiments designed to test the effects of drugs on coronary outflow or inflow; the problem is a composite one, involving an understanding of altered hemodynamics no less than the vascular actions that particular drugs may have. In studies utilizing the perfused heart, the dynamics of ventricular contraction are decidedly abnormal; the nervous supply to the vessels is severed; and doses are frequently employed that are precluded for human use. In studying the coronary sinus flow from intact hearts, these difficulties are avoided, but the danger exists, despite apparent evidence to the contrary, that the same aliquot part of the total coronary flow is not always drained away. Consequently the magnitude of, and perhaps even the directional changes in, flow may not be correctly indicated. While such difficulties appear to have been overcome by measurements of mean total inflow in specially designed perfused preparations or by application of Rein's thermostromuhr to an unopened coronary vessel, it must be evident that effects of drugs on coronary flow so established necessarily apply to changes of flow in distributing branches of the vessel studied and give no information as to improvement or impairment of collateral flow to an ischemic area.

Suppose as diagrammatized in Fig. 1, vessel *A* supplies an area of the myocardium denoted by *A′* and connects through collaterals *C* with another vessel, *B*. Following occlusion of vessel *A*, the only source from which area *A′* could receive blood would be through collateral channels schematically indicated at *C*. This single diagrammatic connection may be allowed to represent either intercoronary, extracoronary, or arterioventricular communications. It should be obvious that most of our knowledge regarding the pharmacological action of drugs applies to effects produced on branches of vessel *A* and gives no information regarding changes in caliber of collateral vessels represented by *C*.

The only attempt to evaluate such actions are the recent studies of Fowler, Hurewitz, and Smith,[1] who observed the changes in color of an

*From the Department of Physiology, Western Reserve University Medical School.
†This investigation has been made with the assistance of a grant from the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association.

ischemic area and compared the size of infarcts following ligation of a coronary branch in animals left untreated with those to whom various drugs had been administered. The problem has apparently not been approached from hemodynamic angles owing to the fact that no criterion of changes in collateral coronary flow has been developed. It was our purpose therefore first to examine the reliability of a number of possible criteria that suggested themselves to us and to draw conclusions regarding the effectiveness or ineffectiveness of a limited number of drugs in promoting a better collateral flow to ischemic areas.

In this report a number of possible expedients tried but found unserviceable will first be reported briefly and then a method that seems to have some merit will be detailed.

BLOOD FLOW FROM A PERIPHERAL CORONARY BRANCH AS A CRITERION

It is known to many experimenters that when a coronary ramus is ligated and the peripheral end is opened, blood oozes from the vessel.

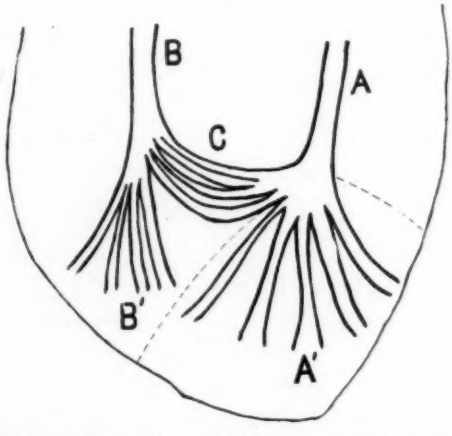

Fig. 1.—Schematic diagram illustrating relation of possible communications with any coronary branch. Discussion in text.

This blood must come from collateral sources. Many observers, including Anrep and Haüsler,[2] and ourselves, had gained the impression that opening such a vessel tends to reduce the chance of fibrillation or of hypodynamic ventricular action. It proved easy for all of us to reach the conclusion, based on impression rather than experimental facts, that this is a collateral flow which is sufficient to maintain the normality of the area affected by coronary ligation. An examination of the facts necessitates the conclusion that such apparently beneficial effects either were not real or were fortuitous.

1. The blood issuing from a cut peripheral coronary vessel is red in color and cannot therefore have yielded oxygen for maintenance of contractions. This suggests that (referring to Fig. 1) blood flowing through collaterals *C* leaves the cut end of *A* and does not pass through intramural vessels *A′* at all.

2. The quantity of blood that flows from the peripheral end of the ramus descendens anterior, when measured in heparinized dogs by means of a horizontal micropipette, is exceedingly small—i.e., is of the order of 0.5 to 0.7 c.c. per minute. Flow rates that even approach those reported by Anrep and Haüsler[2] from the peripheral end of the left circumflex ramus were never encountered from the peripheral end of the ramus descendens. It requires no calculations to conclude that such a small flow would be of insignificant value for a working left ventricle even if its oxygen were completely utilized.

3. Since Tennant and Wiggers[3] had shown that occlusion of the ramus descendens anterior results within one minute in failure of contraction in the ischemic area, the expedient of simultaneously opening the peripheral end was tried, but no beneficial effect could be detected; failure of contraction occurred just as quickly. This offers unqualified proof of the inadequacy of the collateral flow, even when the vessel is opened.

The small magnitude of the flow and the difficulty of registering variations in the minute changes that occurred with alterations in blood pressure and heart rate made it apparent that such a criterion was too hazardous a one for determining whether these collateral channels can be opened sufficiently by drugs to make the collateral supply of functional value.

CHANGES IN PERIPHERAL CORONARY PRESSURE AS A CRITERION

During the early phases of our studies we saw no reason for questioning the view generally held that the pressure in a peripheral coronary vessel represents the pressure transmitted through various collaterals (Fig. 1, *C*) and that it constitutes the pressure head for flow through vessels *A′* when vessel *A* is occluded. It therefore appeared logical to suppose that, if the peripheral coronary pressure increases as a result of drug actions, a greater pressure head is created from collateral sources, regardless of whether this results from elevating pressure in the main branch *B* or from reducing the resistance in collaterals *C*. With vessel *A* occluded, the flow through intramural vessels would never be greater than such a rise of pressure indicated, although it might be less.

Experiments.—As a criterion of changes in collateral flow we first utilized comparative changes in mean carotid and peripheral coronary pressures recorded by properly damped mercurial manometers with carefully controlled hydrostatic levels. After opening the dog's chest, the ramus descendens anterior was ligated, and the peripheral end was cannulated and connected to a mercury manometer. Through a side tube the cannula was occasionally flushed with a small stream of oxygenated Locke's solution to which heparin had been added. This aided in prevention of fibrillation as well as coagulation. However, when fibrillation occurred, the heart could generally be revived by application of

about 1 amp. AC directly to the heart through padded moist electrodes. In many instances revival was accomplished four or six times without obvious harm to the circulation.

TABLE I

EXPERIMENT	AORTIC PRESSURE	CORONARY PRESSURE	APPROXIMATE PER CENT C OF A PRESSURE	HEART RATE
83	80- 86	16-18	20-21	182
84	102-104	26-27	25	167
87	109-114	27-29	25	217
88	75- 77	15	20	165
89	82- 87	21-23	26	190
90	81- 85	25	29-31	214
91	96-102	20-22	21-22	161
92	90- 96	26-28	29	167
93	102-104	23-24	23	174
94	83- 89	22-23	26	131
95	103-112	19-20	18-18.5	169
96	81- 84	22	26-27	153
97	82- 84	27-29	33-35	144
100	96- 97	11-12	11.5-12	179
104	82- 98	17-21	20-21	147
105	108-109	17-18	16-16.5	197
107	60- 80	16-17	21-27	183
111	110-116	30-32	27-28	170

The results of eighteen experiments incorporated in Table I show that, when mean aortic pressure ranged from 68 to 116 mm. Hg, the extreme ranges of peripheral coronary pressure were between 11 and 32 mm. Hg or, otherwise expressed, equaled 11 to 35 per cent of aortic pressure. In twelve instances it equaled from one-fifth to one-fourth the systemic arterial pressure—ratios that may be regarded as roughly approximating that of average dogs under normal conditions. If this really represents collateral pressure, it should be quite adequate to sustain the area deprived of its normal supply.

Since many drugs acting upon coronary vessels produce changes in blood pressure and heart rate, the extent to which these influences alter peripheral coronary pressure needed to be studied. A few of the results are incorporated in Table II. The relationship to systemic pressure, when the latter was elevated either by compressing the aorta or through stimulation of afferent nerves, was studied in fifteen dogs. Consistently peripheral coronary pressure rose and fell with aortic pressure although the ratio of aortic to peripheral coronary pressure sometimes increased with a rise in pressure (cf. Experiments 78, 88, 92, 93, 107, Table II). No differences were noted between experiments in which the increase in aortic resistance was produced by mechanical aortic compression and those in which it was caused by general reflex vasoconstriction. Heart rate changes were produced by stimulating a peripheral end of the right vagus nerve and by rhythmic excitation of the right auricle, the resulting changes in blood pressure being compensated by graded compression of the thoracic aorta. Table II also shows results of a few such experi-

TABLE II

ABRIDGED DATA SHOWING RELATIONS OF MEAN AORTIC AND MEAN PERIPHERAL CORONARY PRESSURES WHEN AORTIC PRESSURE AND HEART RATE WERE VARIED SEPARATELY

EXPERIMENT	AORTIC PRESSURE	PERIPHERAL CORONARY PRESSURE	RATIO	HEART RATE PER MINUTE	REMARKS
78	76*	18	4.2	133	Control
	100*	25	4.0	139	Aortic compression
	184*	35	5.3	124	Aortic compression
	80*	18	4.4	113	Compression released
	140*	27	5.2	114*	Central vagus stimulation
	77*	24	3.2	136	Control after
	146*	35	4.2	138*	Control after
	161*	41	3.9	161	Control after
87	113	20	5.7	60*	Vagus stimulation
	108	22	4.9	115*	After
	115	29	4.0	217*	Artificial stimulation auricle
	132	25	5.3	109†	Control
	132	32	4.1	179†	Artificial stimulation auricle
	125	25	5.0	111*	Control
	127	30	4.2	194*	Artificial stimulation auricle
88	100	29	3.5	161*	Aorta partially compressed
	87*	28	3.1	150	Aorta released
	114*	30	3.7	150	Aorta partially compressed
	88*	28	3.1	150	Aorta released
	100	24	4.2	125*	Peripheral vagus stimulation
	100	36	2.8	185*	After
89	92	32	2.9	185*	Control
	92	26	3.5	106*	Peripheral vagus stimulation
	96	25	3.8	96*	Peripheral vagus stimulation
	96	36	2.7	187*	After
92	129*	40	3.2	167	
	107*	34	3.1	167	
	38*	16	2.4	155	Spontaneous circulatory failure
	100*	26	3.8	150*	Aortic compression
	100	20	5.0	84*	Peripheral vagus stimulation
93	66*	22	3.0	103	Pilocarpine slowing
	102*	27	3.8	106*	Plus aortic compression
	100†	28	3.6	156*	Natural recovery
	102	27	3.8	114*	Peripheral vagus stimulation
	102	30	3.4	181*	After
	54†	23	2.3	142	Circulatory failure
107	60*	16	3.8	177	Control
	80	17	4.7	183	Venous infusion
	112*	27	4.2	187	

*Denotes changes to which attention should be specifically directed.

†Denotes two sets of figures to be especially compared, independent of those marked by the asterisk.

ments. They seem to show that, whenever the heart beats change from an initially high to lower rate, the peripheral coronary pressure tends to lessen (cf. Experiments 88, 89, 92, Table II); and vice versa, when the rate increases, it tends to rise (cf. Experiments 78, 87, 93). Since aortic pressure in all of these instances remains practically unchanged, the ratio of aortic to peripheral coronary pressure decreases as the heart accelerates.

With these effects of changes in systemic blood pressure and heart rate as a guide, the consequences of a number of drugs up to and often exceeding therapeutic doses were studied. In reviewing a large collection of records there was found no single instance in which (a) inhalation of amyl nitrite, 50 per cent oxygen, 6 to 10 per cent carbon dioxide or (b) intravenous injections of sodium nitrite, nitroglycerin, theobromine, aminophylline, alcohol, pitressin, epinephrine, or synephrin produced any change that could not be attributed to changes in arterial pressures. When systemic pressure did not change or when it was compensated by aortic compression or decompression, peripheral coronary pressures remained unaffected.

A strict interpretation of such results in accordance with the generally accepted view that peripheral coronary pressure represents transmitted collateral pressure would lead to the conclusion that no evidence exists that collateral flow is affected by drugs in any way other than through changes in general blood pressure, i.e., drugs causing a fall of arterial pressure reduce collateral flow; those increasing it augment the flow.

Another interpretation proved more probable, viz., that such peripheral coronary pressures *are due not to transmitted pressure* but to compressing action of the ventricle upon intramural vessels and therefore do not serve as an index of collateral coronary flow. These conclusions were arrived at as a result of complicated dynamic studies the details of which are published elsewhere. In brief, Gregg, Green, and Wiggers[4] meanwhile made the discovery that the initial rise of peripheral coronary pressure occurs previous to elevation of the aortic pressure pulse and that at the very beginning of diastole it falls rapidly to a low level, not gradually as arterial pulses do. These temporal differences alone preclude the assumption that variations of pressure in the peripheral coronary vessel are occasioned by transmission of arterial pressure waves. Furthermore, optical curves showed that the rise in peripheral coronary pressure that follows elevation of aortic pressure due to aortic compression is due chiefly to greater rises of individual pressure pulses during the period of isometric contraction. This indicates that the concordant rise of mean peripheral coronary and aortic pressures is fortuitous and that changes in peripheral coronary pressure are related primarily to increase in intramural tension and only to higher aortic pressure so far as this augments the contractile stress of the left ventricle. With such revision of our concepts regarding the significance of peripheral coronary pressure, its use as a criterion of coronary collateral flow had to be abandoned.

CHANGES IN INFLOW RATE AS A CRITERION

The idea occurred to us that changes in the coronary inflow rate of a perfused branch of the intact heart can be used not only as a criterion of flow changes through its distributing intramural branches but of changes in collateral supply as well. The principle can be easily un-

derstood by reference to Fig. 1. If branch *A* be ligated and the peripheral end be perfused with Locke's solution at a pressure *equal to the aortic pressure,* then the pressure in vessels *A* and *B* will be essentially equal and opposite; no flow occurs through channels *C;* and the perfusion fluid must drain through vessels in area *A'*. If the caliber of the latter changes or their average muscular compression alters as a result of drugs added to the perfusion fluid, the rate of flow into vessel *A* should change.

If, on the contrary, vessel *A* be perfused at pressures considerably above the aortic pressure, the runoff from vessel *A* could occur either through *A'* or *C*. If now pressure in the perfused branch be reduced to a low level, e.g., 20 to 30 mm. Hg, *while a drug is injected into the general circulation,* an opportunity should be given for it to pass from vessel *B* by collateral channels *C* into the terminals of *A*. If drugs injected into the general circulation reach and act either upon vessels *C* or *A'*, the inflow rate into vessel *A* at pressures considerably above aortic should alter—increasing if the resistance were reduced and decreasing if it had been decreased.

During the time that these experiments were actually carried out, we were convinced that changes in vascular resistance induced by drugs could probably be referred solely to vascular changes because the ischemic region studied was not contracting. The assumption made that changes of extravascular tension could not be concerned proved untenable, however, as our studies continued. Gregg, Green, and Wiggers[4] found that peripheral coronary resistance is increased just about as much when the area is stretched by the force of intraventricular tension as when it develops tension through its own contraction. Continuing these studies, we found that the degree of systolic stretch and the mechanical increase in peripheral coronary resistance ran approximately parallel to changes in intraventricular tension. Thus all increased during each systole when arterial pressures were elevated as a result of aortic compression or reflex general vasoconstriction, and all decreased during each systole when arterial pressure declined as a result of reflex general dilatation or hemorrhage. Similar complicating effects would doubtless occur during the use of drugs with pressor or depressor effects on general blood pressure. Furthermore, even when aortic pressures were but slightly affected by drugs such as those of the methyl purine group, the possibility that heart rate changes might modify resistance could not be excluded.

These complications were unfortunate in that the method appears unsuitable as a criterion for determining alterations of collateral flow to an ischemic area, following use of drugs. They were fortunate because it does offer a criterion of the changes in resistance to flow which are the resultant of vasomotor and extravascular effects, which ines-

capably operate together when a drug is administered. Since the conditions resemble those following coronary occlusion in man, the actions discovered should be of considerable practical importance.

Experimental Application of the Principle.—Several procedures could be used to record the rate of flow into a peripheral coronary vessel. We devised a method which measured the time required for 1 or 2 c.c. of Locke's solution to flow under pressures declining between fixed levels, near but above mean aortic pressure. A schematic diagram of the apparatus is shown in Fig. 2. Oxygenated Locke's solution at body temperature from a "constant pressure" bottle was continuously perfused through the cannulated ramus descendens, *C*, by use of a shunt, *E*.

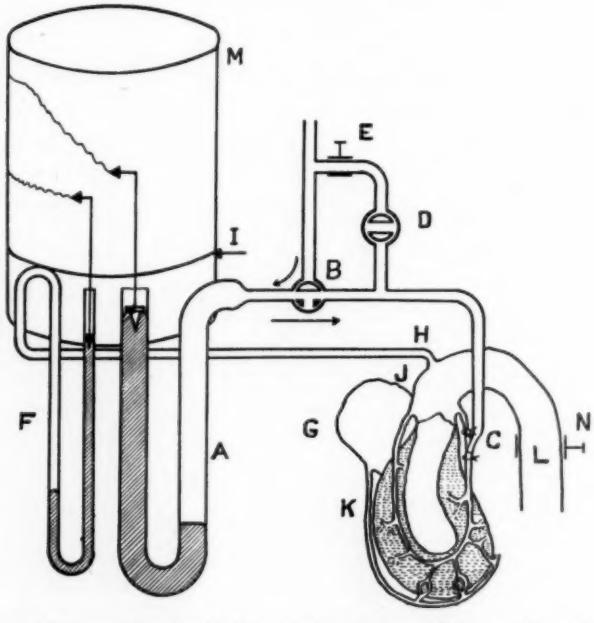

Fig. 2.—Scheme of apparatus for testing coronary flow after possible action of drugs on collateral flow. Discussion in text.

While this flow continued, Locke's solution from the same source was introduced by a three-way stopcock, *B*, communicating with the mercury manometer, *A*, until the mercury and its float had risen to 180 or 200 mm. Hg. The limbs of this manometer were of such size that every centimeter rise or fall of the stylus writing upon the drum represented a volume change of 1 c.c. in the manometer and, of course, a 20 mm. Hg pressure change.

A flow test was carried out by closing stopcock, *D*, and turning stopcock, *B*, simultaneously so that Locke's solution from manometer, *A*, flowed at gradually declining pressure through cannula, *C*, while the kymograph drum, *M*, moved at an even speed. Time was recorded in

0.2 sec. The carotid or subclavian mean pressure was simultaneously recorded by another mercury manometer, *F*. Meticulous care was exercised to have the zero levels of the two manometers exactly the same.

The temperature of the perfusion fluid was maintained constant by submerging the entire manometer, *A*, and all connecting tubes to within a short distance of the cannula in a water-bath, thermostatically controlled.

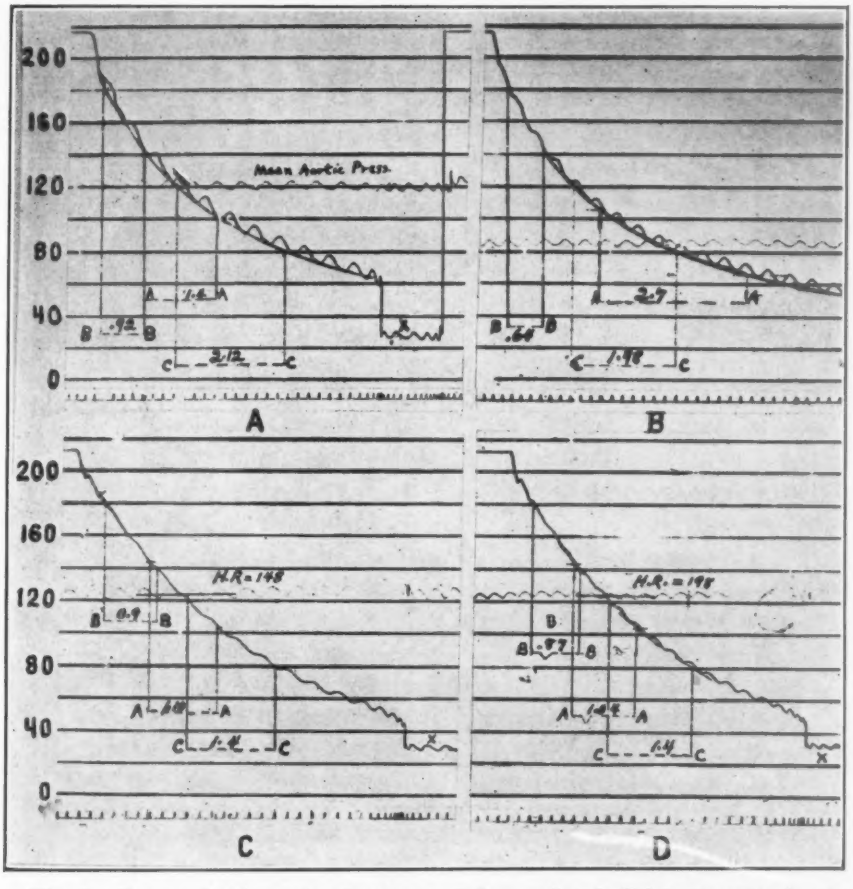

Fig. 3.—Curves showing rate of coronary inflow under declining pressures in relation to mean aortic pressure.
A, control; *B*, after sodium nitrite; *C*, control; *D*, after theamin. Ordinates, mm. Hg. Analysis in text.

Each experiment consisted in determining the control inflow rates three or four times under declining pressures. After the last of these control tests, the pressure was allowed to come into equilibrium with peripheral coronary pressure by keeping stopcock, *D*, closed, thus reduplicating conditions that exist during coronary occlusion. A drug was then administered, care being taken to give it at such a rate that arterial mean pressure was altered as little as possible. After one to

three minutes—or sooner when definite evidence of its action upon the circulation was otherwise evident—a number of flow determinations were repeated in succession.

Method of Analyzing Reactions of a Typical Experiment.—Curves *A* and *B* of Fig. 3 serve as specimen records of results before and after administration of 3 c.c. of 10 per cent sodium nitrite solution. The curve of Fig. 3, *A*—one of three controls—shows in addition to mean aortic pressure, the parabolic decrease in inflow rate as the perfusion pressure declines from 200+ mm. to about 60 mm. Since mean blood pressure was about 120 mm. Hg, the time required for 2 c.c. to flow between a pressure drop from 140 > 100 mm. Hg was first determined at distance *A* – *A*. This equaled 1.40 sec. and denotes the rate of runoff at existing mean pressure. To be quite certain that some runoff from any existing collaterals (Fig. 1, *C*) would be included, the rate of inflow was also determined at considerably higher pressures, viz., from 180 > 140 mm. Hg (*B* – *B* = 0.92 sec.). To establish still a lower range in which runoff from any existing collaterals would be less likely to occur, the time required for flow between 120 > 80 mm. Hg was determined as *C* – *C*, which equaled 2.12 seconds. The pressure was then allowed to seek its level at 27 mm. Hg as shown at *X*. During this time sodium nitrite was administered via a femoral vein. It caused a typical fall in mean pressure. As soon as the maximum drop had been attained the record of Fig. 3, *B* was taken. Since the mean pressure had fallen to 84 mm. Hg, the flow rate at 84 ± 20 mm. was again determined as distance *A* – *A*. As expected, this increased the runoff time for 2 c.c. to 2.7 sec. Calculated on a flow per minute basis, the flow approximately decreased from 85 to 44 c.c. per minute. Since collateral pressure also decreased, the only effect on collateral flow could be a decrease regardless of whether the drug reached and acted upon the vessels. Such observations effectively demonstrate the fallacy of the idea that coronary dilation accompanied by lower arterial pressure can improve blood flow. To determine whether the drug had any effect on peripheral coronary resistance, the rate of flow during the pressure drops from 180 > 140 mm. Hg and from 120 > 80 mm. Hg was determined as before. They are indicated at *B* – *B* and *C* – *C*, respectively. Measurement showed that the duration of *B* – *B* was 0.62 sec. and of *C* – *C*, 1.98 sec. This amounted to an increase in the runoff *B* – *B* from 130 c.c. per minute to 187 c.c. per minute, and in the case of *C* – *C* from 56 c.c. per minute to 60 c.c. per minute. This one of our most favorable reactions denoted a slight decrease in peripheral resistance to runoff at high equivalent pressures.

The action of other drugs was analyzed in a similar way, and the results as regards comparative runoffs at high pressures (*B* – *B*) may be briefly described.

Effects of Drugs Causing No or Insignificant Changes in Mean Arterial Pressures.—In two experiments 200 mg. of theobromine sodium acetate increased the flow from 91 to 105 c.c. per minute in one and decreased it from 105 to 94.3 c.c. per minute in another.

In three experiments from 15 to 60 mg. of monoethanolamine-theophylline (theamin, Lilly) increased the minute flow insignificantly, as follows: 83 < 85 c.c. per minute, 85 < 90 c.c. per minute; 67 < 74 c.c. per minute. Figure 3 *C* and *D* illustrates the very insignificant increase in flow rates of one such test following use of 85 mg. of theamin.

In one experiment 15 mg. theophylline sodium acetate decreased the flow slightly from 73 to 70.6 c.c. per minute.

Ethylenediamine-theophylline (aminophyllin, Searle) was tested in two experiments, but, as the controls failed to check, no positive conclusions may be drawn.

Intravenous infusion of small and large volumes of 10 per cent alcohol produced no discoverable change in three tests. The conclusion cannot be escaped that neither theophylline compounds nor alcohol produces a favorable combination of dynamic effects leading to significant improvement of collateral flow.

Effects of Drugs Causing a Fall in Mean Arterial Pressure.—Sodium nitrite was administered in eight experiments in doses ranging from 20 to 240 mg. The changes in $B-B$ flow were either nil, or a slight augmentation resulted. The latter may be illustrated by the following values: 54.3 < 60.6 c.c. per minute; 151 < 171 c.c. per minute; 166 < 181 c.c. per minute; 187 < 193 c.c. per minute. Whether these changes can be attributed to vasodilation or are due to decreased extravascular resistance caused by lesser tension developed by the ventricle remains undetermined. In any event such slight reduction in resistance could scarcely be important in producing a better blood supply under conditions in the body, for as arterial pressures fall, the pressure head in the supplying artery (Fig. 1 *B*) would also decrease. Calculations of flow rates at perfusion pressures ± 20 mm. of aortic pressure ($A-A$ flows) always showed a marked reduction. The conclusion was drawn that there is no evidence that the collateral supply is increased by use of the nitrite group. The slight reduction in resistance to flow at equivalent testing pressures is probably due to decreased extraarterial compression of coronary vessels following lowered arterial pressure and decreased stretch of the ischemic area. This slightly beneficial effect is more than offset, however, by the lowering of pressure in other branches from which collateral flow could be derived.

Effect of Drugs Causing a Rise in Mean Pressure.—In six experiments 5 to 10 per cent carbon dioxide was administered with oxygen, and the mean pressure rose slightly as a result. The flow effects were negligible. In some cases they consisted in a slight increase; in others a slight de-

crease as is evident from the following effects on $B - B$ flow: $104 < 111$; $161 \rightarrow 161$; $154 < 167$; $240 > 200$; $200 > 181$; $142 < 181$ c.c. per minute.

In three experiments the animal was partially asphyxiated by discontinuing the artificial respiration. A consistent slight decrease in minute flow occurred each time.

Epinephrine in concentrations of 1:400,000 to 1:50,000 was administered very slowly. In nine tests only a slight reduction in flow was

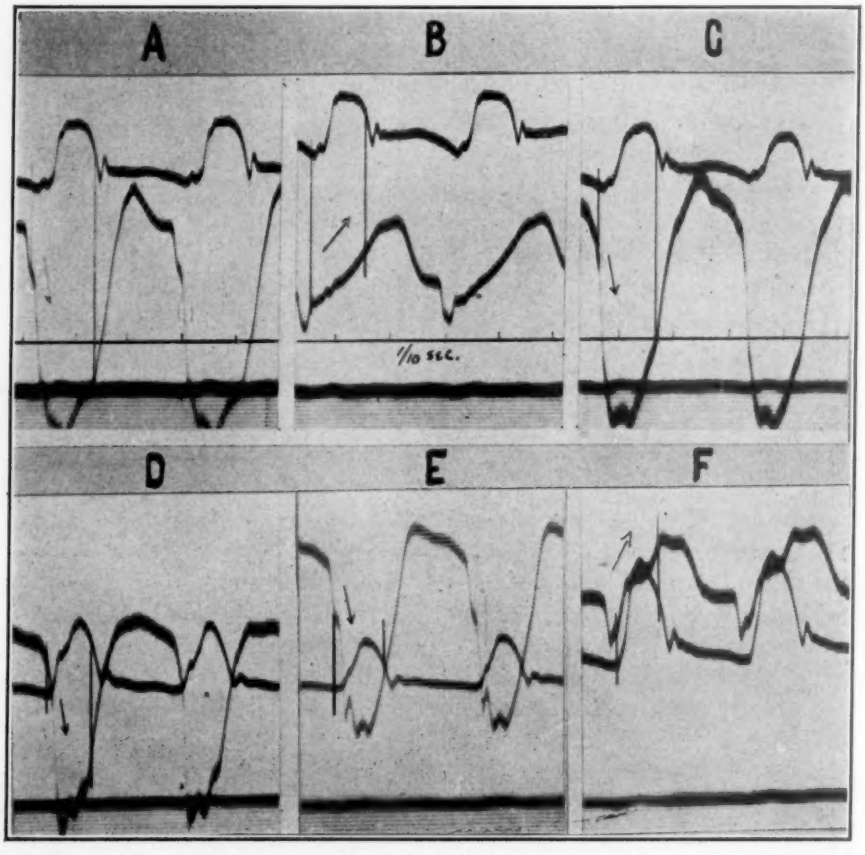

Fig. 4.—Six segments of records showing behavior of a ventricular area studied myographically (lower curve) and aortic pressure (upper curve). Arrows pointing downward denote expansion of area during systole, those pointing upward denote contraction. Discussion in text.

found as indicated by the following data: $42.5 > 38.5$ c.c. per minute; $78.5 > 75.5$ c.c. per minute; $70 < 79 > 59$ c.c. per minute; $101 > 87$ c.c. per minute; $92 > 83$ c.c. per minute; $109 > 92$ c.c. per minute; $157.5 \rightarrow 157.5$ c.c. per minute.

In eight experiments synephrin tartrate also consistently produced a decrease in volume flow, e.g., $76.0 > 65.5$ c.c. per minute; $83.0 > 70$ c.c. per minute; $76.5 > 57$ c.c. per minute; $103.5 > 101.5$ c.c. per minute;

65 → 65 c.c. per minute; 163.5 > 100 c.c. per minute; 130 > 100 c.c. per minute; 75 > 60.5 c.c. per minute.

Such a sampling of drugs having a dilating action on coronary vessels under uncomplicated conditions does not encourage the belief that the collateral blood supply to an ischemic area can be significantly improved by use of any drug.

EFFECT OF DRUGS ON MYOGRAPHIC CHANGES IN THE ISCHEMIC AREA

The myographic demonstration by Tennant and Wiggers[3] that the muscular area supplied by the ramus descendens ceases to contract and vigorously expands within about one minute after occlusion of its supplying branch indicates that the collateral supply which normally exists is not sufficient to maintain contraction of that region of the ventricle. If any drugs act to increase the collateral supply significantly, their injec-

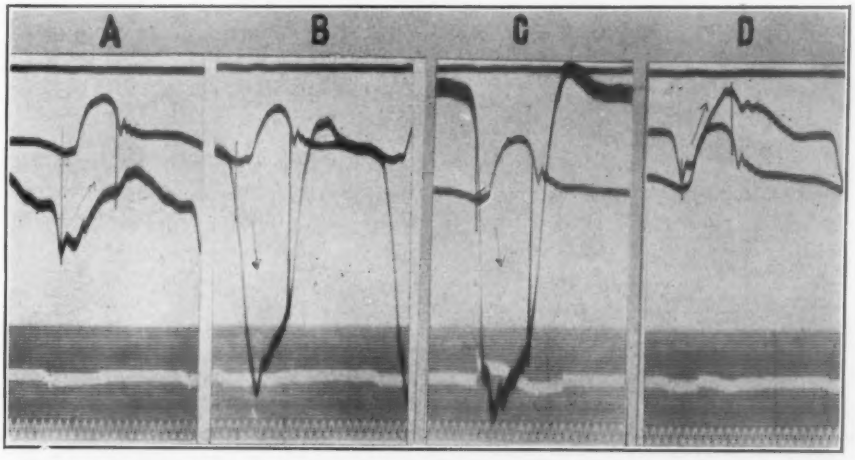

Fig. 5.—Curves similar to those in Fig. 4. The electrographic record should be ignored. Time, 0.02 sec. Discussion in text.

tion, from 1 to 2 minutes after occlusion, should cause some amelioration of the systolic muscular expansion and perhaps some sign of contractile recovery, such as promptly follows unclamping of the main artery.

Experiments.—A myograph connected to a segment capsule was applied as described by Tennant and Wiggers. Aortic pressure was recorded simultaneously. Two series of sample curves indicating the character of responses are shown in Figs. 4 and 5. Figure 4 *A* illustrates the expansion of the ischemic area induced 2 minutes after a preliminary trial clamping of the ramus descendens anterior. Segment *B* illustrates the degree of recovery 1 minute 20 seconds after unclamping the vessel. Segment *C* again shows that the expansion induced by a second clamping is still present 2 minutes 28 seconds after 14 mg. ethylenediaminetheophylline (aminophyllin ampules, Searle) had been injected into a femoral vein. This was followed by a decline of aortic pressure as illus-

trated in segment *D* taken 3 minutes later. No suggestion of contractile recovery exists; the degree of systolic distention is merely less, due to the less vigorous action of the left ventricle. At this time an additional 10 mg. of the drug was given, and 2 minutes later the record of segment *E* obtained in which the myogram was shifted for convenience by adjustment of the Frank capsule only. No evidence of a restoration of contraction exists. Three minutes later the ramus descendens was released, and 1 minute 15 seconds later the record of segment *F* was recorded. Though recovery is not quite complete, evidence of good contraction occurs upon restoration of the normal blood supply.

Similar results were obtained from eight similar trials of various theophylline preparations, all indicating that the collateral circulation is certainly not improved sufficiently by any of these preparations to restore contractions.

Figure 5 *A* shows a normal shortening in the myographic curve and *B* illustrates the pronounced systolic stretching exactly 1 minute after occlusion of the ramus descendens anterior. Segment *C* shows the continued systolic stretching 2 minutes after administration of 30 mg. adenylic acid. As no reversal occurred for 6 minutes, the vessel was unclamped, and curves of segment *D* were recorded 1 minute later. Since improved blood supply promptly restores contraction, but adenylic acid in five trials on different animals showed no sign of such recovery, its potency to augment collateral blood supply must be negligible.

In a similar manner we tested the action of amyl nitrite, sodium nitrite, ouabain, rebreathing pure oxygen, and the effects of hypercapnia. In no single instance was any suggestion of contractile recovery noted.

The experiments were also varied by administering the various drugs just before coronary occlusion (from 30 sec. to 2 min.). It was found, however, that contractions ceased just as promptly after coronary occlusion as without medication.

SUMMARY AND CONCLUSIONS

Valid experimental evidence as to whether a drug can improve collateral blood flow to an ischemic area is difficult to obtain. Observation of color changes or comparison of size of infarcts without and with use of a drug are subject to too many contingencies to have a certain value. Observations as to the effects of drugs upon coronary inflow and outflow do not test the response of collateral vessels and ignore the hemodynamic alterations resulting from occlusion of the main branch.

We therefore studied the reliability of four other possible criteria of changes in collateral flow, viz., (1) changes in rate of blood flow from a peripheral coronary ramus; (2) alterations in mean peripheral coronary pressure; (3) changes in inflow rate at high perfusion pressures before and after use of drugs—the latter being administered during a period

when the area was not perfused; and (4) the ability of drugs given by inhalation or intravenously to prevent contractile failure after ligating a ramus or of restoring such contractions in an ischemic area.

Evidence and reasons are presented why the first and second of the methods cannot be used as criteria. The third method also proved to be no criterion of changes in collateral flow alone but is useful because the flow changes are a *resultant* of vascular and extravascular factors which modify resistance to flow. The following results were obtained:

1. Drugs of the theobromine and theophylline group have a very insignificant effect on flow through an ischemic region.

2. The nitrite group causes a slight decrease in coronary resistance within the ischemic area, but it appears more probable that this is due to attendant reductions of intraventricular tension rather than to effects of drugs reaching the vessels of an ischemic area. At any event this slightly beneficial action is more than offset by the fact that the driving pressure in larger collateral vessels in the left ventricle is reduced.

3. Pressor drugs such as epinephrine and synephrin consistently increased resistance to inflow in the ischemic area. If these drugs exert a dilating vascular action, it is overpowered by greater extravascular pressures in intact hearts.

The fourth method offers conclusive evidence as to whether collateral blood supply increases to a degree to be of functional use. This is ultimately the important question. Our results show that the abolition of contraction about one minute after occlusion of the ramus descendens anterior is not modified in the least by inhalation of oxygen, carbon dioxide, amyl nitrite, or by therapeutic intravenous doses of various theophylline preparations, nitrites, adenylic acid or epinephrine.

A sufficient sampling of possible useful drugs by these methods necessitates, we regret, the conclusion that an increase in collateral circulation sufficient to be of functional use cannot be attained by use of vasodilating drugs after complete coronary occlusion.

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THE PARADOX OF CHIARI'S NETWORK

Review and Report of a Case of Chiari's Network Ensnaring a Large Embolus*

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IT IS hoped that the title of this paper will stimulate interest in a cardiac anomaly which is not exactly rare but concerning which there is little general knowledge. In 1929, I published an article entitled "Variations and Anomalies of the Venous Valves of the Right Atrium of the Human Heart." This article was a review of the knowledge of the subject and report of an original study of the variations and anomalies of these valves in 120 routinely collected hearts, all of which would be considered developmentally normal. A eustachian valve, or valve of the inferior vena cava, was found to be present in some form in all but seventeen of these hearts. A thebesian valve, or valve of the coronary sinus, was found to be present in some form in all but thirteen of them. These figures indicate well the high incidence of such venous valves, which may be considered therefore normal parts of the adult human heart, although they vary greatly in structure and apparently serve no useful purpose in the economy of the extrauterine life of the heart.

EMBRYOLOGY OF THE VENOUS VALVES

Both the eustachian valve and the thebesian valve are remnants of the right valve of the sinus venosus. In the embryonic development of the heart, according to the works of His, Born, and Röse, the single atrial cavity is divided into its two definitive chambers in the following manner: The septum primum arises from the middorsal wall of the atrium and eventually fuses with the endocardial cushions at the junction of the atrial and ventricular cavities. Perforation of the septum primum occurs to form the foramen ovale. This is subsequently closed by the fusion of the left valve of the sinus venosus and the septum secundum which appears in close proximity to the septum primum as an outgrowth from the ventral and caudal wall of the right atrium (Fig. 1).

The right horn of the sinus venosus lags somewhat and is taken up in the wall of the right atrium, which causes the opening into the right atrium of the superior and inferior venae cavae. The right valve of the sinus venosus at one time nearly divides the right atrium into two chambers; but later it becomes progressively lower, its cephalic portion remaining as the crista terminalis, its caudal portion being divided to form the valve of the inferior vena cava (eustachian valve) and the

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valve of the coronary sinus (thebesian valve). As the left horn of the sinus venosus is migrating across the posterior wall of the atrium during the stage of absorption of the remainder of the sinus, it projects into the lumen of the atrium as the inferior sinus septum and divides the caudal portion of the right sinus valve into these two definitive valves. The opening of the left horn of the sinus venosus is the left duct of Cuvier, which is thus pulled over to a place beneath the orifice of the inferior vena cava and persists in part as the coronary sinus. The septum spurium is a vertical ridge formed by a fusion of the right and the left valves of the sinus venosus on the dorsal and cephalic wall of the right atrium, and this is also taken up into the wall of the atrium as it expands. It remains partly, however, to form the uppermost portion of the crista terminalis, where it separates sharply the orifice of the superior vena cava from the atrial appendage.

The eustachian valve serves to direct the blood in embryonic life from the inferior vena cava into the left atrium through the foramen ovale.

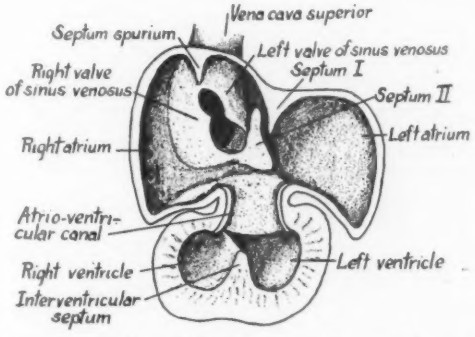

Fig. 1.—Inner view of dorsal wall of heart of 10 mm. human embryo. Drawn from a Ziegler model of one of His's embryos (after Jordan, H. E., and Kindred, J. E.: Textbook of Embryology, New York, 1926, D. Appleton and Co.).

The thebesian valve possibly serves to prevent regurgitation of blood into the coronary sinus during auricular systole. This supposition, however, seems unlikely, since the thebesian valve is usually incompetent, that is, it is not sufficiently extensive to close the orifice of the coronary sinus, or if so, is usually fenestrated.

DESCRIPTION OF THE ADULT VALVES

The eustachian valve is usually a muscular and membranous fold in the right atrium extending posteriorly from below the fossa ovalis and then upward just anterior to the orifice of the inferior vena cava, in the upper portion of which it is lost. Its free margin is concave and directed upward and forward, its adherent border convex and directed downward and backward. One of its surfaces is turned laterally toward the atrium, the other medially toward the vessel. The lower portion is a transverse muscular ridge (the sinus septum) continuous with the limbus

fossae ovalis; the upper portion is usually membranous. Often the membranous part of the valve contains thin strands of ordinary cardiac muscle, especially in its attached portion. Often, also, it has fenestrae, and sometimes thin strands of endocardium are attached at points along its edge or form a little network there. The valve is usually not more than a centimeter wide in the adult. In some cases the eustachian valve is very inconspicuous or may be entirely lacking. In others it may be very broad and project far into the right atrium. Sometimes it is thin and flabby, sometimes fibrous and taut.

The thebesian valve is directly below the lower portion of the eustachian valve in the space between this and the edge of the atrioventricular foramen at the junction point of the lower portion of the interatrial septum and the posterior wall of the atrium in close association with the

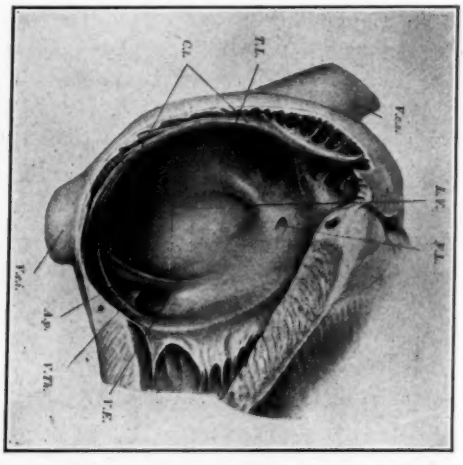

Fig. 2.—Right atrium with the lateral wall removed to show the relationship of the orifices of the atrium and the usual forms of the eustachian and thebesian valves; *V.E.*, eustachian valve; *V.Th.*, thebesian valve; *A.P.*, auricula posterior; *V.c.i.*, inferior vena cava; *C.t.*, crista terminalis; *T.L.*, tuberculum loweri; *V.c.s.*, superior vena cava; *L.V.*, limbus Vieussenii; *F.L.*, foramen Lannelongeus (after Tandler, Julius, in Bardeleben: Handbuch der Anatomie des Herzens, Jena, 1913, Gustav Fischer).

mouth of the coronary sinus, to which it is usually placed laterally. It is frequently semilunar or crescentic, with its anterior free edge concave and its posterior attached edge convex. It is often fenestrated or made up of a network of threads. In fact, its size and form are extremely variable. It may be absent or represented merely by a thin, narrow ridge on the posterior edge of the mouth of the coronary sinus, or it may be present as a large membrane completely covering the sinus orifice. It may even be anterior to the orifice, placed obliquely, transversely or vertically across it. Usually it is very thin and translucent. Sometimes there is a definite connection between it and the eustachian valve. The orifice of the coronary sinus with its valve often lies in a saccular depression between the lower portion of the eustachian valve

and the atrioventricular rim; this is the appendix auricularis posterior of His or the subeustachian sinus of Keith. Figure 2 shows the most frequent form of the valves and their relationships in the atrial cavity.

ANOMALIES OF THE VALVES OF THE RIGHT ATRIUM

Anomalies of these valves are dependent on the degree of completeness of regression of the right and left valves of the sinus venosus, the septum spurium, and the sinus septum. Hearts with defective development of the interatrial septum may contain all grades of persistency of these four structures, but the completely developed heart presents relatively few types of anomalies of the valves. In the adult heart rudiments of the right venous valve are found at the sharp anterior rim of the orifice of the inferior vena cava, extending upward to the upper portion of the crista terminalis and downward across the orifice of the coronary sinus toward the tricuspid orifice. Remnants of the left venous valve are located on the interatrial septum in the posterior region of the annulus fossae ovalis and the intervenous tubercle (tuberculum loweri), which is merely an eminence superior to the fossa ovalis between the orifices of the venae cavae. Residual structures of the septum spurium would be found anterior to the mouth of the superior vena cava near the interatrial septum. Remnants of the sinus septum are seen normally in the muscular ridge which extends from the lower end of the limbus fossae ovalis to the inferior part of the rim of the orifice of the inferior vena cava and becomes a part of the normal eustachian valve. If the inferior sinus septum merely fuses with the right venous valve and does not divide it, the eustachian and thebesian valves are formed as a continuous fold with an attachment to the wall of the atrium in the region of the inferior sinus septum. Should the inferior sinus septum fail entirely, the two valves will be a simple membrane or reticulum unattached except perhaps posteriorly to the wall of the atrium.

CHIARI'S NETWORK

It is not my purpose in this paper to mention every article ever written upon the variations and anomalies of the venous valves of the right atrium. Since 1865, when Lindes described the malformed heart of a newborn infant with persistence of the right and left venous valves, there have been twenty-nine publications on this subject, an average of one article every two and one-half years. Since my review in 1929 of all previous articles, there have been three additional reports (Hueper and Berghoff, Alvarez and Herrmann, and Helwig). Particular interest has been taken in an anomaly of these valves known as Chiari's network. In 1897 H. Chiari reported eleven cases of an anomaly consisting of a network of fine or coarse fibers in the right atrium, its attachments extending from the interatrial septum or upper portion of the crista terminalis to the thebesian and eustachian valves or to the region of the

orifices of the coronary sinus and inferior vena cava. In one case the network was responsible for the death of the patient, a young man of twenty-four. There was extensive pulmonary embolism, the source of which was apparently a thrombus which had formed in the confluence of the fibers of the network. In eight others the network was incidental, although three of the patients died of heart disease.* None of Chiari's cases showed any other relevant congenital anomalies.

Since Chiari's description of the network, 25 instances of a similar formation have been reported (A. Weber, 1; LeCount, 1; Looser, 1; Ebbinghaus, 1; Thilo, 2; Haas, 1; F. P. Weber, 2; Jordan, 2; Yater, 4; Hueper and Berghoff, 2; Alvarez and Herrmann, 1; Helwig, 7). In addition to these Mönckeberg states that in Düsseldorf in two years he observed 6 typical examples of Chiari's network in persons aged from twenty-four to fifty-nine years. He did not, however, describe these cases. This anomaly occurs probably in between 2 and 3 per cent of hearts.

The designation, Chiari's network, should be confined, probably, to those reticula in connection with the eustachian and thebesian valves which have threads attached in the upper region of the right atrium, near the crista terminalis, or to the interatrial septum in the region of the tuberculum loweri.

This formation does not usually cause a murmur, although Alvarez and Herrmann attributed to such a network a peculiar, low pitched "thonging" hum heard along the right sternal border from the third rib downward, mainly in diastole. However, this was accompanied by the diastolic murmur of aortic regurgitation due to syphilitic aortitis with involvement of the aortic valve.

Method of Opening Heart to Preserve Network.—In a heart opened in the usual routine manner, the eustachian valve is cut almost directly through its middle by the scissors as it passes between the orifices of the two venae cavae. If a network is present, the cut fibers collapse against the wall of the atrium and are not usually observed upon inspection of the atrial cavity. To preserve the network one should open the right atrium by an incision into its wall just above and parallel to the atrioventricular junction without cutting the rim of the orifice of the inferior vena cava. The incision may be extended to the tip of the atrial appendage. It is well to look through the open end of the inferior vena cava before making the incision in order to determine whether a network exists.

THE PARADOX OF CHIARI'S NETWORK

The reason for this designation is that, although probably not often of clinical importance, the network in some cases may be responsible for death from pulmonary embolism, while in others it may prevent death

*In two cases the cause of death was not given.

from this cause. In a certain number of cases there is noted an increased facility for the formation of thrombi on the fibrous threads of the network. In the literature nine instances are recorded in which such thrombi were present, and in one (Chiari's Case 1) there was no doubt that the thrombus was the cause of fatal pulmonary embolism. In one of my cases also the patient died of pulmonary embolism, but there was, in addition, extensive thrombosis of several large veins, which were probably the real source of the embolus. In another case of mine there was an embolus in the left pulmonary artery, the only discoverable source of which was a large thrombus surrounding the threads of the eustachian valve. This patient, however, did not die as the result of pulmonary embolism. On the other hand, as was beautifully illustrated by Haas's case, the reticulum may ensnare an embolus reaching the right atrium from a large vein and so obviate serious pulmonary embolism. Haas's patient was a man, aged fifty-seven years, who died of cerebral embolism. There were mitral stenosis, thrombosis of the left femoral vein, and embolic infarcts of the lungs. The right atrium was dilated, and in a semilunar line surrounding the orifices of the coronary sinus and inferior and superior venae cavae were attached three groups of three or four fibrous threads each, which coalesced to form the three main threads of a network. On the net formed by the three main threads hung an embolus 6 cm. long and surrounded twice in its middle by a thread. This embolus undoubtedly came from the thrombus in the femoral vein, and one end showed the irregular surface where it had broken off. The network had ensnared this huge embolus and prevented fatal pulmonary embolism. The case reported below was similar in a general way to this case of Haas's.

REPORT OF CASE

The patient, P. L., a white man aged thirty-nine years, entered Georgetown University Hospital on Sept. 5, 1935. From June 19 until July 4, and again from August 11 until September 2, 1935, he had been a patient in another hospital. He claimed he had had pulmonary tuberculosis in 1918 and had completely recovered therefrom. For years he had suffered from severe pain in the region of the right sacroiliac joint. On June 15, 1935, he had suddenly developed precordial pain which radiated to both arms and was accentuated by exercise and deep inspiration. Examination in the first hospital did not reveal the cause of this pain. The physical examination was negative, and urinalysis, hemogram, roentgenogram of the chest, and electrocardiogram* were reported essentially normal. The temperature was elevated for a week, the highest recorded being 103° F., after which it went occasionally as high as 99.6° F. The pulse rate varied proportionally. The respiratory rate was at first moderately elevated. Although a diagnosis was not made, it is probable that the condition was acute myocardial infarction of the posterior basal region of the left ventricle.

Until his second admission to the same hospital in August, the patient was apparently well. He entered this time in order to have an operation on his back. On

*Restudy of the electrocardiogram, which was made on June 23, reveals early changes suggestive of the T_3 type of acute myocardial infarction.

the day of operation, Aug. 12, 1935, the temperature was 99.4° F., the pulse rate 64, and the respiratory rate 20. Under ethylene and ether anesthesia, partial removal of the right lumbosacral facet was done through an incision over the right posterior superior iliac spine. The operation was apparently successful since he never complained of the pain in the back thereafter. However, from August 13 until discharge an irregular fever was recorded. At times the temperature went as low as 97° F., at other times it rose as high as 103.8° F., the pulse rate varying proportionally. On August 20 he complained of a pain along the lower left costal margin. On August 22 a note was made that there was left pleural effusion with thickening of the pleura near the base. The blood pressure dropped from 120 to 96 systolic and from 80 to 68 diastolic. There was a slight cough. The respiratory rate varied from 20 to 32, but on that night it rose to 56 and then slowly decreased until nearly normal to the time of leaving the hospital, September 2. Sputum examination, agglutination tests, and other laboratory examinations were essentially normal. During the three days at home the patient had more sharp pains in the chest, now on both sides, associated with severe dyspnea. Cough with bloody sputum developed, and the temperature rose to 104° F.

On admission to the Georgetown University Hospital, Sept. 5, 1935, he presented the clinical picture of pneumonia. The temperature was 101.2° F., the pulse rate 124 and regular, and the respiratory rate 54. There were diminished tactile fremitus, marked dullness and reduced intensity of the breath sounds and a few inspiratory subcrepitant râles over both lower lobes posteriorly up to the fourth ribs, and especially in the left axilla. The blood pressure was 130 systolic and 76 diastolic. A roentgenogram of the chest made with a portable machine showed infiltration at both lung bases and possible atelectasis of the left lower lobe. Urinalysis revealed albumin, graded three-plus, hyaline and granular casts, graded one-plus, and erythrocytes, graded one-plus. A hemogram showed 79 per cent hemoglobin (Newcomer method), and the erythrocytes numbered 4,370,000 and the leucocytes 17,300 per cubic millimeter of blood. Polymorphonuclear neutrophiles constituted 88 per cent of the latter. At first some blood was expectorated, but after the second day cough did not recur. Until death on Oct. 1, 1935, the course was very stormy. At one period tympanites was distressing but was relieved by injections of prostigmin and by enemas. Delirium was present most of the time. The temperature varied between 101° and 103° F., the pulse rate between 120 and 130 and the respiratory rate between 30 and 50. The cardiac rhythm was always regular, and there was never a murmur audible. The blood pressure most of the time was over 100 systolic and 65 diastolic, but the day of death it dropped to 80 systolic and 42 diastolic. On September 6 and for three days thereafter a severe pain was complained of in the right lower axillary region, but a definite pleural friction rub could not be elicited. The physical signs in the lungs progressed to those of definite areas of consolidation with numerous subcrepitant râles in both lower lobes. Dysfunction of the urinary bladder with retention of urine was troublesome for a few days. The patient was very restless and responded very poorly to sedatives and hypnotic drugs, but most of the time he ate and drank well. A second roentgenogram of the chest was reported to reveal bilateral bronchopneumonia. The hemogram did not alter much. Several blood transfusions were given, and the patient was kept in an oxygen tent intermittently. Edema of the extremities was not present at any time. Near the end moderate cyanosis appeared. The heart continued to beat, but irregularly and slowly, for several minutes after respiration ceased. Seven weeks had elapsed from the time of the operation until death occurred.

Necropsy.—Only essential findings revealed at necropsy will be recorded. There was moderate cyanosis, and the veins of the neck were distended. Upon removing the breastplate extensive and relatively recent fibrous pleural adhesions were noted in both pleural cavities. These were more dense over both lower lobes and especially

on the right side. Small subpleural hemorrhages were numerous. There was no fluid in either hemithorax. The lower lobes of both lungs were practically solid, while the upper lobes and the right middle lobe presented almost normal crepitation. On sectioning the lungs the consolidated portions were found to consist of a number of grayish, granular infarcts, about 2.5 by 4 cm. across, apparently of different ages but seemingly mostly of several weeks' duration. The pulmonary arteries of the affected lobes and of the right upper lobe were filled with emboli, some of which were apparently undergoing organization.

The heart was distended with blood, especially the right side. There were numerous subepicardial petechiae. Upon opening it by the method described and removing post-mortem blood clots a very interesting picture was revealed (Fig. 3). In the right atrium was a large embolus ensnared in a Chiari's network. The embolus,

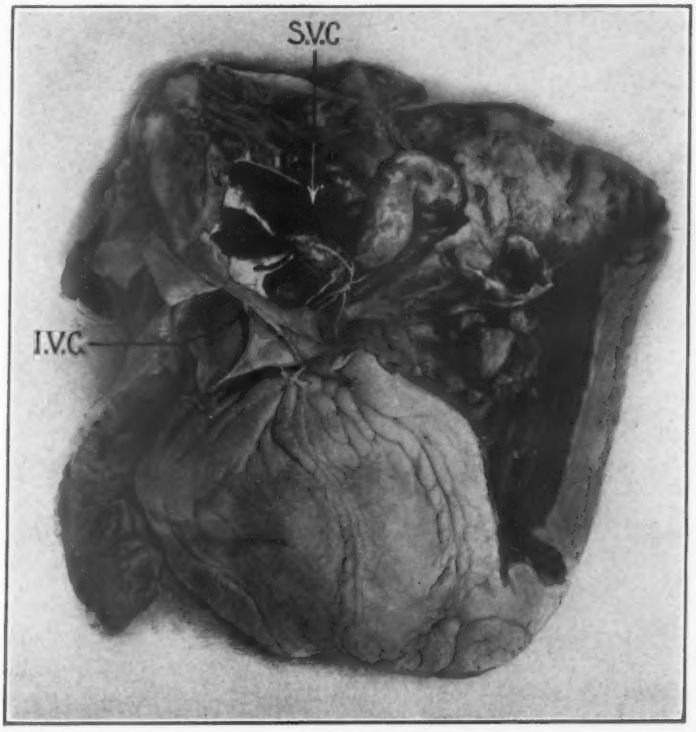

Fig. 3.—Opened right atrium and ventricle, showing the large embolus ensnared by a Chiari's network. Numerous mural thrombi are present in both the atrium and the ventricle. *S.V.C.*, orifice of superior vena cava; *I.V.C.*, orifice of inferior vena cava.

which was curled up like a pig's tail, was mainly grayish. It was 11.5 cm. long, and its thickness varied from 0.9 to 1.6 cm. That portion nearest the inferior vena cava for about 1.5 cm. was caught in the network. There were four sets of fibrous threads which contributed to the network. A narrow rim of thin fibrous tissue constituted the eustachian valve, which ended below in the sinus septum and continued above into a narrower rim of thin fibrous tissue which was attached to the lateral wall and roof of the atrium just medial to the crista terminalis and anterior to the orifice of the superior vena cava, medial to which it faded out in the interatrial septum. The uppermost portion of the network came from a broad expansion of the lateral portion of this rim and contributed the broadest thread of all. The next lower part of the network was derived from the eustachian valve just

anterior to the orifice of the inferior vena cava and consisted of three threads arising close together from the edge of the valve. Three more delicate threads arose from the sinus septum, the muscular ridge between the orifice of the inferior vena cava and the orifice of the coronary sinus. A few fine threads represented the thebesian valve, and an isolated one of these passed upward to join the network. The exact architecture of the network could not be determined because the threads were wrapped about and fused with the embolus. Apparently some of the threads were several centimeters long. Light grayish yellow mural thrombi of various sizes and shapes were intimately attached to the wall of the atrium. A large one on the posterior portion of the wall above the orifice of the inferior vena cava was 2 cm. in width and was elevated 1.3 cm. A large irregular one partly filled the atrial appendage. Smaller thrombi were attached to other portions of the wall. These resembled vegetations superficially. A row of these was attached to the crista terminalis, and a small one was attached to the upper thread of the network near its origin. Several small thrombi were present between the pectinate muscles. Most of these thrombi appeared to be covered by endothelium. The wall of the right atrium was definitely hypertrophied, being 0.35 cm. thick just above the atrioventricular junction. The tricuspid valve appeared normal. The right ventricle was also definitely hypertrophied and measured 0.55 cm. in its upper part. There were several large irregular thrombi projecting from the anterior and septal walls of the right ventricle, the largest ones being just below the tricuspid valve and around the so-called moderator band, which was well developed. The pulmonary valve and the main pulmonary artery appeared normal.

The coronary arteries showed significant changes. The anterior descending branch of the left was moderately sclerotic, but the lumen was not much compromised. The circumflex branch of the left for about 3 cm. was filled with a firm thrombus. Marginal branches of this artery were moderately sclerotic. The right coronary artery and its branches showed less degeneration than the left. The average thickness of the left ventricle was 1.2 cm. The myocardium appeared to be normal except for a scar in the uppermost part of the posterior wall. This scar involved the whole thickness of the wall and narrowed it in an area of about 2 by 3 cm. The left atrium, mitral valve, aortic valve, and aorta appeared to be normal.

The spleen was normal in size but very soft. It contained a small infarct under its capsule. A small Meckel's diverticulum was found, and there were two partially gangrenous appendices epiploicae with twisted pedicles. The gallbladder was the seat of cholesterosis. There were aberrant vessels to the kidneys. Otherwise the abdominal viscera were apparently essentially normal.

A search for the origin of the emboli in the heart and lungs revealed that the right femoral vein, beginning about 10 cm. from its origin, was filled with a firm, dry, red thrombus for a distance of over 15 cm. This extended into the main tributaries of the vein. The greatest part of the thrombus was not adherent to the walls of the veins, and the intima of the veins was smooth.

Microscopic study revealed that the largest mural thrombus in the right atrium was covered, in part at least, with a sheath of endothelial cells, apparently originating from the endocardium. Beneath this was a rim of delicate avascular reticulum. The thrombus was composed mainly of fibrin, the erythrocytes and leucocytes having disappeared. Scattered through the thrombus were large pale cells with ovoid nuclei. The endocardium adjacent to the thrombus was altered and contained some histiocytes and lymphocytes. The myocardium below this was essentially normal.

Sections of most of the large coronary arteries showed various degrees of sclerosis and atheromatosis. The degeneration was mainly intimal and subintimal. The lumina were not greatly compromised except in the portion of the left circumflex artery which was filled with an organized thrombus containing endothelial-lined

spaces partly filled with erythrocytes. The scar in the upper posterior wall of the left ventricle appeared to be the result of infarction. There were many thin-walled blood vessels distended with blood in portions of the scar. Sections of other portions of the myocardium did not reveal any abnormality.

Sections through several of the pulmonary arteries containing emboli showed different pictures. One embolus showed no organization although endothelium had grown around part of it. Another was well organized in its periphery, and the wall of the artery was somewhat degenerated. Still another showed greater organization. The infarcts in the lungs were typical anemic infarcts.

A section through the lower portion of the right femoral vein showed the vein to be filled with a lamellated clot, at the periphery of which was a very narrow zone of very early organization. The wall of the vein was moderately degenerated, the muscle fibers being separated and fibroblasts invading the wall in places. A smaller tributary vein was quite similar. The femoral artery showed Mönckeberg's sclerosis, with irregular deposition of calcium in the middle zone of the media. Some histiocytes were present here and there at the edge of the calcium. Sections of all other organs were of no great interest.

DISCUSSION OF CASE

Points of interest in the case were the large embolus ensnared in the Chiari's network, the numerous mural thrombi in the right atrium and right ventricle, the pulmonary emboli and infarcts, the asymptomatic femoral thrombosis, the hypertrophy of the right atrium and ventricle, the organized and canalized thrombus in the sclerotic left circumflex artery, and the scar in the upper posterior wall of the left ventricle. In the last few months of life the patient apparently had an idiopathic thrombophilia. The first thrombotic episode was probably in June, at which time it is presumed that thrombosis of the circumflex branch of the left coronary artery occurred. Recovery followed, but after the "clean" operation on his spine in August thrombosis occurred also in a large vein, probably in the right iliac or femoral. All or part of this thrombus became dislodged and was swept up to the right atrium, where a large section of it was ensnared in the Chiari's network; a section probably went also at this time to the pulmonary arteries. Other thrombi were apparently formed later in the veins but were soon dislodged and swept up to the lungs. Such an assumption seems necessary to explain the absence of symptoms and signs due to occlusion of the large veins. The asymptomatic thrombus found at necropsy in the right femoral vein and its tributaries was undoubtedly of recent origin, as indicated by smoothness of the walls of the veins and the absence of any but the earliest attempt at organization.

The large embolus entrapped in the right atrium was swished about therein and injured the endothelial lining of the atrium. This injury, together with the disturbance of the flow of blood through the atrium and the assumed thrombophilia, was responsible for the formation of the mural thrombi on its wall. Similar thrombi formed also in the right ventricle, apparently because of disturbance of blood flow in its cavity.

Some bits of these thrombi may have broken off and gone to the lungs. The course of the illness suggests also the probability of the presence of a low grade intravascular infection. The degree of toxemia and the softness of the spleen seemed to be greater than the pulmonary infarcts alone might produce. There was never any evidence clinically of cardiac dysfunction. Death resulted apparently from respiratory failure and toxemia.

The case illustrates the rapidity with which hypertrophy of the right atrium and ventricle may develop, inasmuch as the pathological investigation did not reveal any cause for the hypertrophy other than obstruction of the pulmonary arteries by the emboli, which apparently had been there only a few weeks.

SUMMARY AND CONCLUSIONS

1. Venous valves of the right atrium, the eustachian and thebesian, may be considered normal parts of the adult heart. They are remnants of the right venous valve of the sinus venosus of the embryo and serve no useful purpose in extrauterine life.

2. Chiari's network, a reticulum of fibrous threads in connection with these valves with attachments to the crista terminalis and tuberculum loweri, occurs probably in from 2 to 3 per cent of otherwise developmentally normal hearts.

3. Chiari's network produces no symptoms or signs.

4. This network may be the origin of thrombi which may give rise to pulmonary emboli, or it may ensnare emboli from some systemic vein and prevent sudden fatal pulmonary embolism (the paradox of Chiari's network).

5. A case is reported in which death eventually occurred from embolic pulmonary infarcts and low grade infection and in which a Chiari's network had ensnared an embolus 11.5 cm. long originating from an asymptomatic thrombus which had formed in a large vein. The patient apparently had a thrombophilia, since he had just previously had coronary arterial thrombosis and also later developed mural thrombi in the right atrium and ventricle. The case illustrates the rapidity with which hypertrophy of the right atrium and ventricle may occur.

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AURICULOVENTRICULAR DISSOCIATION AND THE ADAMS-STOKES SYNDROME IN ACUTE CORONARY VESSEL CLOSURE*

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THE purpose of this study is to call attention to the clinical course and the graphic manifestations of a consecutive series of fifteen patients who developed auriculoventricular dissociation and the Adams-Stokes syndrome following acute coronary vessel closure. The Adams-Stokes syndrome may be defined as a clinical condition characterized by recurrent attacks of unconsciousness, lasting from eight seconds to several minutes, associated with epileptiform convulsions and stertorous breathing and ending in apnea. During such periods there is a collapse of the circulation with a drop in the blood pressure and absence of the pulse and heart sounds. The term was coined by Huchard[1] who gives credit to both Stokes[2] and Adams[3] for having described the clinical picture in the presence of bradycardia. Burnett[4] and Pletnew,[5] however, cite Morgagni[6] as the first to have observed the phenomenon.

We now know, from an increasing number of carefully correlated observations, that syncopal seizures in patients in whom alterations in the cardiac mechanism are responsible for such attacks may be due, in the main, to (a) stoppage of the whole heart, that is, absence of both auricular and ventricular contractions from direct or reflex stimulation of the nodes of the heart through the vagus or carotid sinus[7-10]; (b) sudden interference with impulse formation in the auriculoventricular node[11-13]; (c) cessation of ventricular contractions in the presence of persistent auricular activity during complete heart-block[14]; and finally (d) the various grades of acceleration of the ventricles that end in transient periods of ventricular fibrillation or flutter.[15]

Mahaim's[16] recent excellent survey of the literature and Geraudel's[17] microscopic studies reveal that the Adams-Stokes syndrome occurs most commonly during auriculoventricular dissociation in the course of the more gradual form of ischemia to the auriculoventricular node of the heart, as a result of arteriosclerotic narrowing of the blood supply to this specific tissue. With the exception of some sporadic observations,[18] a systematic study of the Adams-Stokes syndrome and the outcome of such patients in the course of a sudden closure of a coronary artery is still wanting. A knowledge of the circulation of the node is essential to an understanding of this problem.

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THE CIRCULATION TO THE CONDUCTION MECHANISM OF THE HEART

The auriculoventricular conduction mechanism of the heart consists of a node (Tawara) and a bundle (His) of neuromuscular tissue which bifurcates into two main branches in the region of the upper part of the interventricular septum. The right limb breaks up into an extensive interlacing and interanastomosing network of fibers which are distributed over the internal surface of the right ventricular wall. The left limb passes over the top of the interventricular septum and spreads into a fan-shaped, thin and flat structure and distributes itself over the interior surface of the left ventricle.[19]

The circulation to the auriculoventricular node has its origin in the anterior and posterior interventricular arteries, the former originating from the left coronary and the posterior interventricular from the right coronary. The anterior interventricular artery has its origin in the region where the left coronary bifurcates to give off the circumflex branch of the left, but the posterior cannot be so easily distinguished since it is a continuation of the right circumflex artery.

In approximately 90 per cent of human beings[19-23] the right circumflex branch of the right coronary artery crosses the crux posteriorly and in that region gives off the *ramus septi fibrosi,* which supplies the superior portion of the interventricular septum and sends a branch into the auriculoventricular node, coursing along this as far as the main bundle and the upper part of both bundle branches. Usually, therefore, it is the right coronary artery which furnishes the nutrition for the main portion of the auriculoventricular node, but exceptions are not rare, and the left coronary artery occasionally sends its branches posteriorly to the superior interventricular septal region and in that manner, crossing the crux, becomes the main supply to the node (10 per cent of cases). Nevertheless, the vascularization of the auriculoventricular node may be said to be most usually posterior, no matter from which of the coronary arteries the blood supply originates.

The left branch of the bundle has a double arterial supply. Its anterior ramifications are supplied by a large number of perforating branches from the anterior descending branch of the left, while its posterior ramifications receive their nutrition from the less numerous posterior perforating branches of the right coronary artery.

The right bundle branch, however, receives most of its supply from the anterior perforating branches of the large descending branch of the left. Gross has described a special artery supplying the right bundle branch and has called this the *anterior ramus libri dextri.* According to Cranicianu, in its first portion, the right bundle branch receives its vessels from two superior anterior perforating arteries. In its second portion it is supplied by the same artery as described by Gross, while in its third portion there are additional arterioles which anastomose in this inferior region with arterioles originating in the right coronary.

There is a unanimity of opinion that the sino-auricular node is supplied from the right coronary artery in approximately 60 per cent of the cases and from the left in 40 per cent. The existence of anastomoses between the anterior and posterior perforating arteries of the septum and consequently between the two arteries supplying the auriculoventricular conduction mechanism is well established from anatomical studies.

With these points in view, the following case histories are presented out of a series of fifteen patients with acute coronary vessel closure and Adams-Stokes seizures that I have seen during the past few years. They give an idea of the onset of the symptoms, the clinical course, and the treatment for most of such patients in the course of their illness.

REPORT OF CASES

CASE 1.—L. B., a male, aged sixty-five years, was known to have had hypertension for six years. On Feb. 18, 1935, while sitting in the bathroom, he had a sudden seizure of unconsciousness with convulsions. During the next fifteen minutes until he was seen by a physician, he had several other seizures of stertorous breathing with unconsciousness. In one of these attacks he bit his tongue badly, for when seen he was bleeding from the mouth. His face was intensely cyanotic. His respirations were very irregular. Long periods of apnea alternated with Cheyne-Stokes respirations. His skin was cold and clammy. His heart rate varied between 6 and 46 beats per minute. The heart sounds were barely audible. The lungs were full of moisture. The liver and spleen were not palpable. He was incontinent of feces and of urine. The blood pressure was not obtainable.

Electrocardiograms obtained at this time revealed low voltage, left axis deviation, prominent Q-waves in Leads II and III, and R-T fusion above the isoelectric line in Leads II and III. The ventricular complexes were aberrant in all three leads. The ventricular rate was regular and averaged 38 beats per minute, the auricles beating twice as fast.

The administration of atropine sulphate (gr. 1/75) resulted within seven minutes in an acceleration of the ventricular rate to 76 beats per minute. The further administration of a similar dose resulted in clearing up the moisture in his lungs. Three hours after the onset of his first attack his ventricular rate gradually became lower until, when it reached a level of about 12 to 16 beats per minute, the patient suffered again from an Adams-Stokes seizure. At this time epinephrine hydrochloride (1 c.c. of the 1:1000 solution) was injected intramuscularly and within three minutes there was a return to a regular rhythm, with the ventricles beating at 78 per minute.

Aside from warmth to the body and the administration of hot liquids, the patient received no other medication. Electrocardiograms obtained on the following morning revealed a Q_2-T_2, Q_3-T_3 pattern with marked inversion of the T-waves in all three leads, and this pattern has persisted to the present day.

The patient was kept in bed for six weeks and advised to take a prolonged rest until he was enabled to walk without suffering any signs of shortness of breath. His blood pressure at present is 130/80, and he is up and about, carrying on his work as a normal individual.

CASE 2.*—A. C. G., a male, aged seventy-one years, was known to have had hypertension for at least five years. On March 22, 1931, at 3:00 A.M. he complained of

*I am indebted to Dr. Joseph Levy, of New Rochelle, N. Y., for the electrocardiograms of this patient.

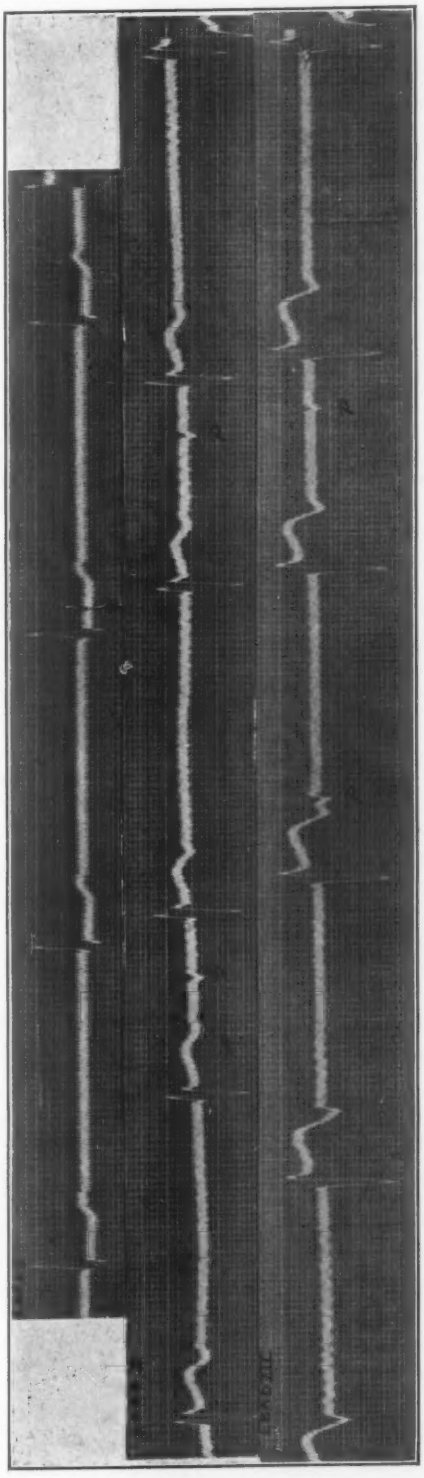

Fig. 1.—An electrocardiogram obtained shortly after and prior to a syncopal attack following an acute coronary vessel closure. Note the irregularity of the ventricles, the slow ventricular rate, and the almost total absence of auricular complexes.

nausea and of pain over the precordial region radiating to the left arm, and he vomited. His blood pressure had dropped from 230/110 to 100/82. Several hours later he became very restless, complained of excruciating pains over the entire chest and developed Cheyne-Stokes respiration. Then he suddenly lapsed into unconsciousness with epileptiform convulsions.

Electrocardiograms obtained at this time and shortly before a major seizure of unconsciousness showed left axis deviation with some slight intraventricular conduction disturbance. Q_3 formed the main ventricular deflection, and in Lead III there was R-T fusion above the isoelectric line. The ventricular rate was totally irregular, the rate varying between 20 and 40 beats per minute, and there was only an occasional P-wave present in the record (Fig. 1).

The injection of atropine sulphate (gr. 1/75) on the following day eliminated the block and accelerated both the auricles and the ventricles, but only for very short periods. Twenty-four hours before death, which occurred three days after the first episode, there was stoppage of the whole heart for periods of from twenty to forty seconds, with typical Adams-Stokes seizures. The repeated administration of epinephrine hydrochloride (1 c.c. of the 1:1000 solution) yielded a slight acceler ation of the ventricular rate but did not prevent recurrences of the syncopal attacks. The patient was desperately sick as he would go from one attack into the other, and no medication seemed to be of any avail. He died in pulmonary edema three days after the onset of his acute coronary vessel closure. No autopsy was obtained.

CASE 3.—M. W. C., an insurance broker, aged sixty-four years, was first seen on the morning of Aug. 6, 1932, at his office, where he was found on the floor in a semistuporous condition. He had been having repeated convulsions, with frothing at the mouth, for about twenty minutes before the arrival of a physician. Examination at this time showed him to be in a semistuporous condition, intensely cyanotic, with blood-tinged froth oozing from both the nares and the mouth. His breathing was irregular. The superficial veins of his neck were markedly distended, and as he was being examined, there were occasional convulsive movements of his left arm, forearm, and face. His eyes had a glassy stare, but he could be easily aroused by supraorbital pressure. The apical impulse of his heart was neither visible nor palpable. The blood pressure was 134/98 and his lungs were full of large bubbling râles. The heart rate was totally irregular and averaged between 16 and 40 beats per minute when counted over a period of several minutes.

An electrocardiogram, obtained while the patient was still on the floor, revealed an irregular slow ventricular rate, averaging 28 beats per minute with auricular fibrillation. The main ventricular deflections showed low voltage, marked intraventricular conduction disturbance, and a tendency toward right axis deviation. This type of complex persisted for the rest of his life (Fig. 2).

On the assumption that the auricles were beating independently of the ventricles at this time because of the slow ventricular rate, even though the rhythm was totally irregular, the patient was given 1 c.c. of epinephrine hydrochloride (1:1000 solution), and within five minutes there was an acceleration of the ventricular rate to 68 beats per minute. The rhythm, however, still remained irregular and auricular fibrillation persisted.

Following this increase in the heart rate, the patient became conscious and could talk coherently. He was removed to his home, put to bed and given hot drinks. His body was kept warm with hot water bottles and warm blankets and he received an injection of atropine sulphate (gr. 1/75) for the relief of his pulmonary edema.

Two hours after his initial seizure, when the heart rate had again returned to a level of 27 beats per minute, he was given another injection of epinephrine hydrochloride (1 c.c. of the 1:1000 solution), and again there was an acceleration of the heart rate to an average of 70 beats per minute.

He received a total of 7 c.c. of epinephrine hydrochloride in a period of seven hours, the injections being given whenever he complained of dizziness or faintness. As a rule, these symptoms invariably coincided with the reduction in his heart rate below 25 beats per minute.

Following that, no other medication was necessary for the next two days. He was then placed on ephedrine sulphate in doses of 30 mg. twice a day and this was increased to three times a day when it was noted that the ventricular rate vacillated

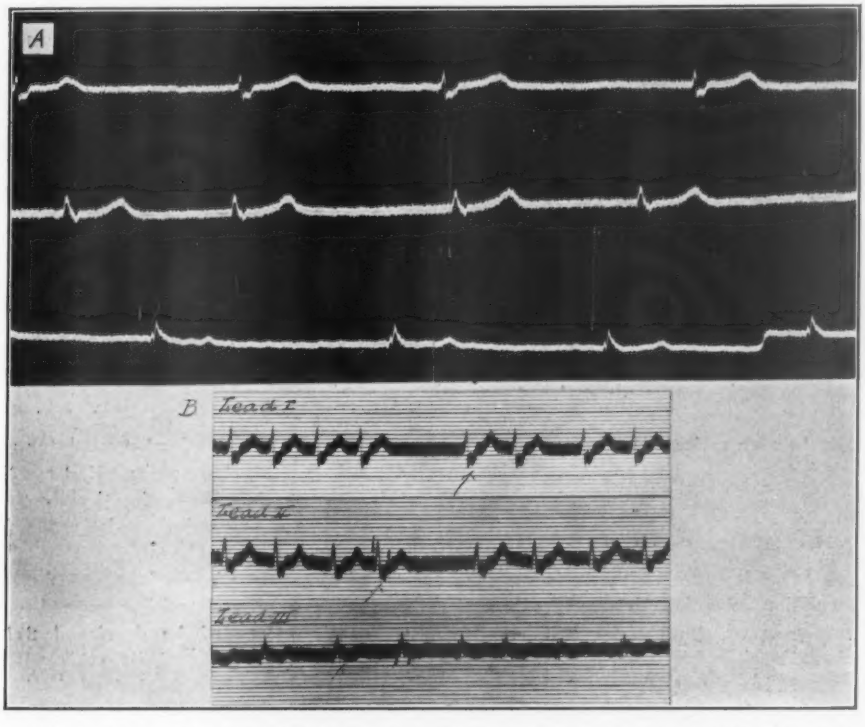

Fig. 2.—*A*, auricular fibrillation with a slow ventricular rate following an acute coronary vessel closure.

B, an increase in the ventricular rate obtained by the administration of epinephrine hydrochloride. Note the intraventricular conduction disturbance in both records.

between 22 and 29 beats per minute. On three doses of this drug per day, his heart rate for the next six weeks averaged about 45 beats per minute. The auricular fibrillation persisted.

Within eight weeks following his initial Adams-Stokes seizure, the patient was out of bed and up and about. His heart sounds were now audible. The blood pressure was 140/65. Fluoroscopic examination of his chest revealed his left ventricle to be concentrically hypertrophied and unusually large. His lungs were moderately congested. The edge of the liver was 6 cm. below the costal margin in the region of the midclavicular line. For the next two years until his death on April 7, 1935, he had recurrent Adams-Stokes seizures only when he omitted the ephedrine from his daily routine. On several occasions when he was studied, omissions of this drug for a period of ten days was followed invariably by a lowering

of the ventricular rate in the presence of auricular fibrillation followed by a syncopal seizure. For his congestive heart failure, he received periodic injections of salyrgan intramuscularly and this, in addition to a salt-poor diet with moderate rest, was sufficient to keep him comfortable. He died suddenly one day while he was walking on the street.

CASE 4.—L. L., a tailor, aged fifty-six years, was first seen on Feb. 9, 1933. About twenty minutes earlier, he had been found in a semistuporous condition on the floor of his shop. He was known to have had high blood pressure for seven years but never complained of any symptoms referable to his heart. When seen shortly after his accident, he was extremely cyanotic, and his respirations were irregular. He was disoriented, and his speech was quite unintelligible. His skin was moist and cold. His pulse was barely palpable. His heart sounds were hardly audible and his systolic blood pressure was 90. The diastolic level could not be obtained even though his ventricular rate was 62 beats per minute at that time.

While being examined on the couch approximately one-half hour after his attack, he suddenly stiffened out, with his hands outstretched and his fists taut. His head turned toward the left, his eyes rolled, his face assumed a pasty pallor, and there were several convulsive movements of his head in the direction opposite the rolling of his eyes. He lost consciousness, stertorous breathing set in, he was incontinent of feces and of urine, and his heart sounds, although barely audible, could still be heard beating at the average of 10 per minute.

An electrocardiogram obtained shortly after this episode revealed left axis deviation, marked intraventricular conduction disturbance, complete auriculoventricular dissociation, with a ventricular rate averaging 35 beats per minute, and the auricles beating irregularly and varying between 40 and 60 beats per minute.

The patient was given 1 c.c. of epinephrine hydrochloride (1:1000 solution), and within five minutes following the injection there was a return to normal rhythm. He became rational and was transferred home. His rhythm remained normal for a period of eight weeks, during which time he received ephedrine sulphate (30 mg.) once a day. When he was given more than this dose per day, he developed systemic manifestations, such as tremors and sweating, so that his dose had to be reduced to the lowest possible level.

After ten weeks, he was up and about and became conscious of an occasional omission of a heartbeat. Electrocardiograms obtained at such a time showed an omission of a complete ventricular cycle. Shortly afterward he developed 2:1 heart-block, with a ventricular rate of 40. It was possible to abolish this with ephedrine sulphate, but he never felt well when his heart was in normal sinus rhythm again. At present, he is up and about, perfectly comfortable on 30 mg. of ephedrine sulphate once a day. On several occasions when he was admitted to the Montefiore Hospital for study, it was possible to demonstrate a very definite relationship between the omission of the drug and a further reduction in the ventricular rate. Whenever the ephedrine was omitted, his heart rate fell below its basic level of 38 beats per minute and he began to complain of dizziness with spots before his eyes. Indeed, on one occasion he developed an Adams-Stokes seizure when the ephedrine sulphate had been omitted for five consecutive days.

Throughout his entire illness, the patient never showed signs of congestive heart failure, such as shortness of breath, enlargement of the liver, or edema of the lower extremities.

CASE 5.—S. G., a clothing salesman, aged fifty-three years, was admitted to the Montefiore Hospital on May 9, 1930, and died on Dec. 20, 1934. His main presenting complaints on admission were associated with a tumor involving the spinal cord in the region of the first down to the level of the fourth dorsal vertebra. He was bedridden most of the time and had no symptoms referable to his heart

until March 2, 1934, at 5:30 P.M. On that afternoon, the patient was seen in a drenching sweat shortly after he had had an attack of projectile vomiting. He said that "things went suddenly black" before his eyes and he had a very severe "inward pressure" below the sternum. He had lost consciousness shortly after

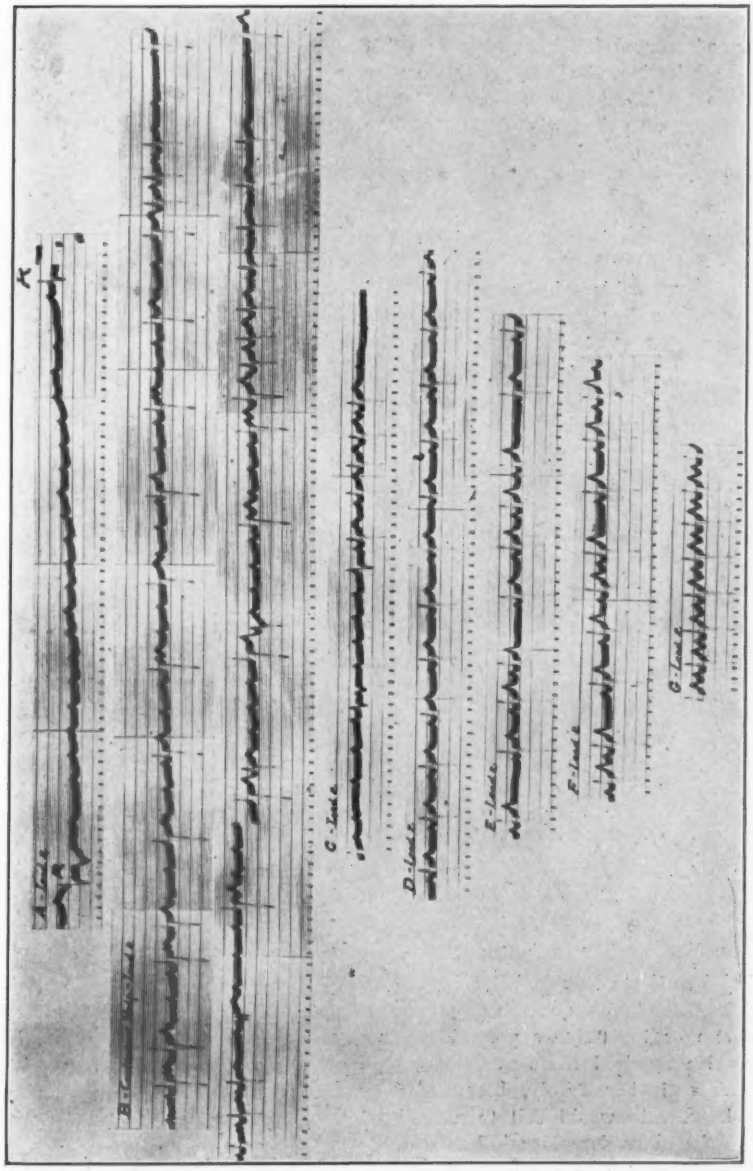

Fig. 3.—*A*, electrocardiograms showing standstill of the ventricles following an acute coronary vessel closure. *B*, a record obtained after the injection of 1 c.c. of the 1:1000 solution of epinephrine hydrochloride. Note the acceleration of the ventricular rate following the injection of the drug, with runs of tachycardia alternating with bradycardia before the final establishment of a normal rhythm, *G*.

that and when seen his peripheral and apical heart rates averaged 28 beats per minute. His blood pressure was 70/40.

While being examined at this time, his heart became progressively slower until it reached a level as low as 6 beats per minute, when the patient again lost consciousness, developed stertorous breathing, became intensely cyanotic, had repeated convulsions, and was incontinent of feces and of urine. Shortly after this unusually

slow ventricular rate of only 5 to 6 beats per minute, the heart rate suddenly became accelerated to 64 beats per minute. For the next half hour he had several typical Adams-Stokes attacks with a marked reduction in the ventricular rate during which time repeated electrocardiograms were obtained of his abnormal cardiac rhythm (Fig. 3).

Following one of these typical attacks of ventricular standstill, the patient was given 1 c.c. of epinephrine hydrochloride (1:1000 solution) and within a minute following the injection, the blood pressure rose to 142/60, and his heart rate was accelerated to 50 beats per minute, but the rhythm was irregular. Following another injection of epinephrine hydrochloride about ten minutes later, his blood pressure rose to 200/70, but his heart rate returned to a normal sinus rhythm after successively going through variable interferences with the conduction mechanism.

For the next few days his temperature was elevated to 101° F., and he suffered several more attacks of syncope associated with epileptiform convulsions, until March 19, 1934, when his apical rate was 60 beats per minute. From then on until the day of death on Dec. 20, 1934, he had normal sinus rhythm.

Autopsy revealed his heart to be markedly enlarged, weighing 520 gm. The pericardial layers were smooth and shiny. The pericardial sac contained 800 c.c. of clear yellowish fluid. On the posterior surface of the left ventricle there was a marked depression in the wall consisting of fibrous tissue. The ventricular walls were thickened, especially in the region of the pulmonary conus. The myocardium of the anterior surface of the left ventricle showed numerous scattered, white, fibrous areas. The coronary arteries were markedly narrowed and presented areas of calcification, but the circumflex branch of the left showed only a tiny pinpoint lumen that led to the infarct on the posterior wall of the left ventricle and the adjacent septum in the region of the auriculoventricular node and its bundle.

Case 6.—C. T., a male, aged sixty-nine years, was admitted to the Montefiore Hospital on Oct. 22, 1931, and died on May 11, 1932. He was known to have had a blood pressure of 280/70 at the Presbyterian Hospital where he had been on several previous occasions in 1929 because of dyspnea, dizziness, swelling of the ankles and abdomen, and vomiting of seven weeks' duration. During one year prior to his admission to the Montefiore Hospital he had been complaining of recurrent precordial pains. In August, 1929, he fainted on the street and, when seen one-half hour after his accident, his heart rate was found to be 16 beats per minute. An electrocardiogram obtained at that time showed marked intraventricular conduction disturbance, right axis deviation, complete auriculoventricular dissociation, with the ventricles beating irregularly and varying between 16 and 28 beats per minute. The auricular rate was regular.

The administration of epinephrine hydrochloride (1 c.c. of the 1:1000 solution) forty minutes following his attack of unconsciousness was associated with a return of the heart rate to 60 beats per minute, and this persisted for several months thereafter. He required repeated doses of diuretics for relief of his congestive heart failure and then finally, because of recurrent attacks of syncope during which his heart rate would fall to a level of 6 to 8 beats per minute, he was admitted to the Montefiore Hospital.

Here it was possible to accelerate his heart rate very readily with epinephrine hydrochloride, but only temporarily. The administration of this drug would invariably produce marked systemic manifestations, even in small doses of 0.25 c.c. of the 1:1000 solution, with a concomitant increase in his heart rate far above the basic level.

He was likewise intolerant of ephedrine, and its administration was invariably followed by precordial pain with an irregular ventricular rate which resembled

very closely the cardiac abnormalities seen to follow the injection of epinephrine in this patient. He died in congestive heart failure, with complete auriculoventricular dissociation.

Autopsy revealed that his heart weighed 550 gm. There were a few pleuropericardial adhesions. There was marked hypertrophy and some dilatation of the left ventricle. The anterior and posterior papillary muscles were flattened and grayish in color. On section they appeared yellowish brown. The mouths of the

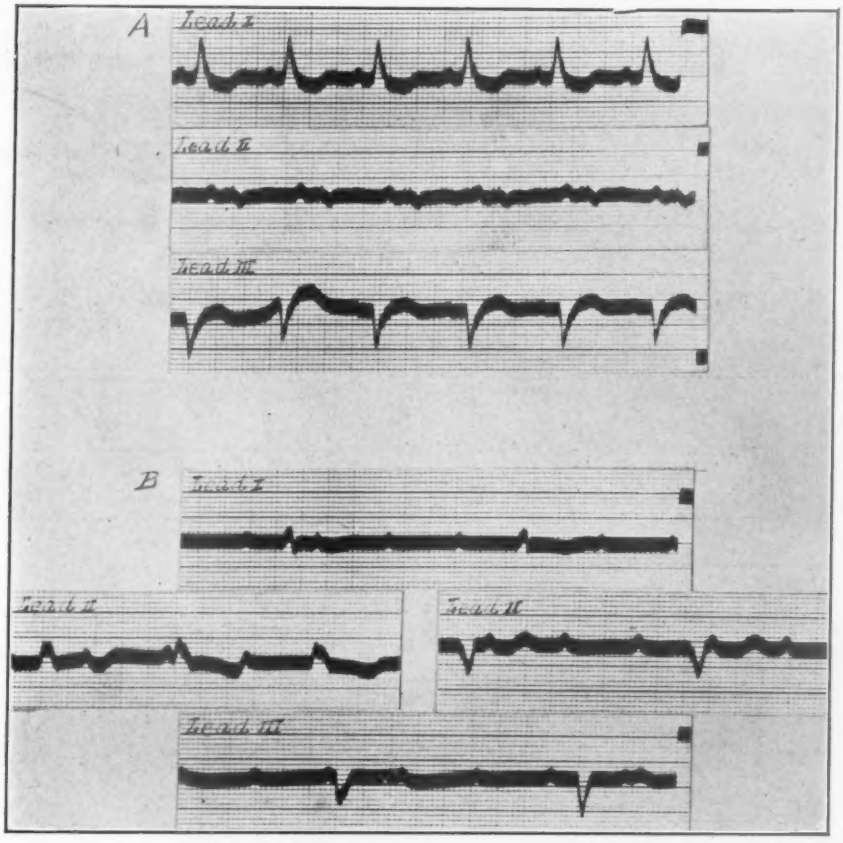

Fig. 4.—*A*, an electrocardiogram showing intraventricular conduction disturbance as a result of myocardial infarction, prior to another acute coronary vessel closure with Adams-Stokes seizures.
B, an electrocardiogram of the same patient obtained after an acute coronary vessel closure with Adams-Stokes seizures. Note the complete auriculoventricular dissociation, the lowered voltage, the irregular ventricular rate, and the change in the direction of the complexes in Lead II.

coronary arteries were patent. There was marked subendocardial fibrosis of the left and right ventricles. The posterior wall of the left ventricle showed a fairly extensive area about 3 cm. in length, extending through the entire thickenss of the myocardium which was grayish yellow in appearance and which was adjacent to an area somewhat reddish in color that looked like a comparatively recent infarct. There was marked atherosclerosis of the descending branch of the left coronary artery. The lumen, however, was patent throughout. The transverse branch of the left coronary artery showed very marked thickening; one portion of the lumen was practically pinpoint in size, and its center was filled with a gelatinous pale gray substance which, on section, turned out to be a recanalized thrombus. The right coronary artery showed no actual occlusion.

DISCUSSION

It is very obvious from these observations that syncopal attacks and complete heart-block are much more commonly associated with an acute coronary vessel closure than has been considered hitherto (Table I). Of the fifteen patients in this series, there were thirteen males and two females; the youngest was fifty-four years and the oldest seventy-one years of age. Each one was known to have had hypertension for a considerable time prior to the development of the acute coronary vessel

TABLE I

SHOWING THE AGE, SEX, ANTECEDENT HISTORY AND ELECTROCARDIOGRAPHIC PATTERNS OF 15 PATIENTS WITH ACUTE CORONARY ARTERY CLOSURE AND THE ADAMS-STOKES SYNDROME

NAME	SEX	AGE	ANTECEDENT HISTORY	E.C.G. FOLLOWING ACUTE CORONARY VESSEL CLOSURE	DURATION OF LIFE AFTER THE ONSET OF ADAMS-STOKES SYNDROME	THE RESTORED CARDIAC RHYTHM
L. B.	M.	65	Hypertension	L.A.D. Low Voltage Q_2, Q_3 Pattern	Living	Sinus rhythm
L. L.	M.	56	Hypertension	R.A.D. Low Voltage I.C.D.*	Living	Complete heart-block
B. S.	F.	58	Hypertension	L.A.D. Q_3 Pattern	Living	Sinus rhythm Transient heart-block
S. L.	M.	68	Hypertension C.H.F.†	Low Voltage I.C.D.	Living	Sinus rhythm
A. L.	M.	58	Hypertension	L.A.D. Low Voltage A.F.	20 months	Sinus rhythm
M.W.C.	M.	64	Hypertension C.H.F.	R.A.D. Low Voltage A.F.	33 months	A.F. Transient heart-block
L. D.	M.	68	Hypertension C.H.F.	R.A.D. Low Voltage I.C.D.	28 months	Sinus rhythm
S. G.	M.	53	Hypertension	L.A.D. I.C.D.	10 months	Sinus rhythm
C. T.	M.	69	Hypertension C.H.F.	R.A.D. I.C.D.	25 months	Sinus rhythm Transient heart-block
F. L.	M.	54	Hypertension	L.A.D. A.F.‡	24 months	Sinus rhythm
F. M.	M.	68	Hypertension	R.A.D. I.C.D.	22 months	Sinus rhythm
R. N.	M.	63	Hypertension Diabetes	L.A.D. Low Voltage I.C.D.	4 days	
S. S.	M.	58	Hypertension	L.A.D. Q_2, Q_3 Pattern	3 days	
A. C. G.	M.	71	Hypertension	L.A.D. Q_3 Pattern	4 days	
B. F.	F.	62	Hypertension	R.A.D. I.C.D.	6 days	

*I.C.D., intraventricular conduction disturbance.
†C.H.F., congestive heart failure.
‡A.F., auricular fibrillation.

closure, and six showed signs of congestive heart failure, presumably from previous myocardial infarcts. Aside from the well-known symptoms and signs that follow a coronary vessel closure, such as precordial pain, shock, vasomotor collapse, fever, leucocytosis, drop in the blood pressure, weak heart sounds, pulmonary edema, and Cheyne-Stokes respiration, they all exhibited, in addition, the Adams-Stokes syndrome.

The auriculoventricular node of the heart over which impulses are transmitted from the auricles to the ventricles is an unusually sensitive structure. Sudden interference with the circulation to this conductive mechanism may result in a disruption of the normal sequence of events from the auricles to the ventricles. The ventricles may suddenly stop contracting before they assume an independent pacemaker of their own. In that event the absence of an adequate cerebral circulation from stoppage of the ventricles may result in an Adams-Stokes seizure, the duration of which will depend upon the periods of ventricular standstill.

Since posterior infarcts in the region of the auriculoventricular node are almost as frequent as anterior infarcts, judging from personal observations on one hundred consecutive patients with coronary artery closure that have come to necropsy at the Montefiore Hospital, it is likely that this mechanism of standstill of the ventricles explains the coma that is so often seen in patients with acute coronary artery closure. Occasionally the auriculoventricular dissociation is of only short duration, varying from a few minutes to several days, depending on whether the artery to the node itself is occluded or whether the node is the seat of an inflammatory reaction from closure of larger radicals away from it. Again there may be an extension of a thrombus from the septal artery to the artery of the bundle, and the block and syncopal attacks may appear a few hours or a few days after the coronary vessel closure.

Repeated syncopal seizures result in a cerebral anoxemia which may so depress the brain centers that after several attacks within only a few minutes, patients remain unconscious for long periods at a time. Indeed, I have seen patients with syncopal attacks from other causes of stoppage of the circulation, stay in coma for as long as twelve hours, despite the return of the basic heart rhythm and rate to normal figures.

As a rule, the size of the posterior infarcts of the left ventricle of the heart are smaller than those of the anterior infarcts. The vessels supplying that region are not of the caliber of those anteriorly. Since most patients exhibiting syncopal attacks apparently recover from their initial accident following closure of the vessels posteriorly, it becomes apparent that such lesions in this region are not so grave as those in other localities of the heart, despite the severity of the symptoms. With increasing age and with the antecedent hypertension which almost all of these patients present, there develops a concomitant diminution in the caliber of the vessels supplying this region of the heart, from the intimal proliferation of the arteriosclerotic process that accompanies the hypertension. It is a gradual narrowing that thus prepares the soil for the

final closure of the artery to the node so that the heart is able to tolerate the trauma much better than if such a process were not there. The smaller the size and caliber of the vessels occluded, the less severe the trauma and the shock.

It seems to me that this is a much more plausible explanation for the recovery of these patients than the development of increasing anastomoses which are described as present in the progressively ageing heart.[19] These anastomoses to the arteries supplying the auriculoventricular node and the bundle in themselves undergo changes in structure similar to those of the main supply of the vessels which are usually occluded, and it is hardly possible to expect them to function through the infarcted area which surrounds the bundle and the conducting mechanism following the closure of the main vessel. Furthermore, since the heart-block persists for some time in the majority of patients who survive the initial shock and trauma, it is very obvious that once the arterial supply is completely occluded and the idioventricular pacemaker assumes a function of its own, it is only when recanalization takes place and the node itself is nourished again by the original arterial supply that normal rhythm is resumed.

I have had the opportunity recently to confirm this belief in a patient who showed heart-block for four years. During all this time the main ventricular deflections of the electrocardiogram were aberrant and resembled those seen in a so-called arborization block. Shortly prior to death she developed normal sinus rhythm, again with complexes of the supraventricular form.

At necropsy the main artery to the bundle which had been thrombosed, showed almost complete recanalization, but the surrounding arterioles entering the region of the bundle were completely obliterated by intimal thickening. The presence of a few fibers in the neuromuscular tissue which had still escaped degeneration by receiving a new blood supply through the recanalized vessel enabled the heart to resume normal sinus rhythm. My own observations on hearts with multiple myocardial infarctions reveal a remarkable absence of anastomosing vessels in the infarcted regions following coronary artery closures. The heart must be nourished in another manner than through anastomoses, or perhaps it does not require as much nourishment in its infarcted state as it does normally. Obviously, the margin of safety is very great. Otherwise we should not have such long survivals of patients with multiple myocardial infarctions of the heart.

THE ELECTROCARDIOGRAM IN PATIENTS WITH COMPLETE HEART-BLOCK AND ADAMS-STOKES SEIZURES FOLLOWING AN ACUTE CORONARY VESSEL CLOSURE

Our conception of the relationship between the arterial supply to the heart, the underlying pathological lesion, and the graphic manifestations noted in the electrocardiogram has changed considerably since

Ball[18] summarized the available literature on the electrocardiograms seen in heart-block following an acute coronary artery closure. We now have sufficient evidence at hand to believe that the electrocardiogram can localize for us the infarcted area in either the anterior or the posterior wall of the left ventricle, regardless of which of the coronary vessels of the heart is occluded.[24, 25, 26]

For such localizations of an infarct it is essential that the main ventricular deflections of the electrocardiograms be of the supraventricular form. They must not show any aberration associated with intraventricular conduction disturbance, either before or after the development of heart-block. Indeed, in the present state of our knowledge, all such records must be excluded when correlation is made between the infarcted area and a specific electrocardiographic pattern. On such a basis, since thirteen of the fifteen patients reported in this study showed marked intraventricular conduction disturbances in the electrocardiogram before, during, and subsequent to an acute coronary artery closure, the records are valueless in localizing either the vessels occluded or the areas in the ventricles that have been infarcted.

On the other hand, it has been pointed out in the anatomical description of the vascular supply to the bundle that no matter which artery supplies the posterior wall of the left ventricle, heart-block invariably results from a closure of a vessel posteriorly. It is therefore fair to conclude, from studies so far, that the presence of Adams-Stokes seizures with dissociation of the auricles from the ventricles results, as a rule, from infarction posteriorly, no matter whether the arterial supply to the conduction mechanism originates from the right or the left coronary artery. The presence of heart-block of this type, then, is of itself enough to localize the lesion in the heart for us, independent of the form, shape, or size of the ventricular deflections and of the T-waves which may follow them.

The autopsy findings in two of our patients support this contention. In both instances, for example, it was the circumflex branch of the left coronary artery that crossed the crux posteriorly in the region of the interventricular septum and supplied the auriculoventricular conduction mechanism. In both instances branches of that artery were occluded and yielded posterior wall infarctions in the region of the interventricular septum and auriculoventricular node. Yet the electrocardiograms showed marked aberration of the ventricular complexes, and because of that the pattern usually associated with posterior infarctions was totally masked. Nevertheless, since both patients showed standstill of the ventricles with the clinical manifestations of acute coronary artery closure and heart-block, the pathological lesion was localized posteriorly on purely anatomical grounds.

A note should be made here of the auricular complexes in the electrocardiograms and the auricular rhythm present shortly after the on-

set of the syncopal attacks and following the acute coronary artery closure in the posterior region of the left ventricle. In one patient (Fig. 1) there was almost a total standstill of the auricles for long periods at a time, only one or two auricular complexes appearing to every six ventricular beats. In several others, auricular fibrillation set in both the transient and the permanent forms. There can hardly be any relationship between these arrhythmias of the auricles and an involvement of the artery supplying the sino-auricular node. Since in normal hearts this sinus node is supplied in 60 per cent of the instances by a stout branch arising in the right coronary artery, one would assume that the changes in the auricular behavior of our patients might be the result of obstruction to the arterial supply to the sinus node. This, however, is a very remote possibility. I have repeatedly seen such changes in the rhythm of the auricles following the asphyxia that results from stoppage of the ventricles. Every type of auricular irregularity may then occur, such as flutter, fibrillation, and tachycardia without any organic changes in the arterial supply to the sinus node. In the majority of all patients such changes in the behavior of the auricles are only transitory and appear after the syncopal attacks, but disappear after resumption of the basic ventricular rhythm.

THE USE OF EPINEPHRINE HYDROCHLORIDE AND EPHEDRINE SULPHATE IN THE TREATMENT AND PREVENTION OF SYNCOPAL ATTACKS FOLLOWING AN ACUTE CORONARY VESSEL CLOSURE

That the injection of epinephrine hydrochloride (1:1000 solution) and the ingestion of ephedrine preparations have a specific action on the conducting mechanism of the heart can no longer be doubted. These drugs may not only yield an increase in the basic ventricular rate during established auriculoventricular dissociation, but can also stimulate the auriculoventricular pacemaker to function in the presence of widespread disease of the node. These drugs must necessarily so sensitize the auriculoventricular conduction mechanism, that even though impairment to the circulation is very definite, the threshold of impulse passage is heightened and because of this, in many instances, it is possible to restore normal sinus rhythm by their use, even though it be for only short intervals at a time. Consequently, despite the presence of coronary artery involvement with infarction of the heart, epinephrine hydrochloride is the drug of choice in patients in whom symptoms arise as a result of impaired circulation to the auriculoventricular node and consequent interference with impulse passage and impulse formation.

Indeed, I feel that without epinephrine injections at a time when stoppage of the ventricles takes place, many patients would succumb to the anoxemia and resulting cerebral trauma in the wake of repeated

syncopal attacks. Each patient, however, must be studied individually and the drugs and their dosages must be so adjusted that no lasting systemic manifestations result from their administration.

As a rule, it is expedient to tide over a patient when he is having his syncopal attacks with repeated intramuscular injections of epinephrine hydrochloride in doses of 1 c.c. of the 1:1000 solution, either until normal rhythm is restored or until the basic level of the heart, during auriculoventricular dissociation, remains fairly fixed, that is, when it does not vary more than five beats per minute. With this basic level relatively stationary, ephedrine sulphate in 30 mg. doses may be substituted orally for the epinephrine. This dose may then be repeated three or four times a day depending on the tolerance of the patient for the drug. The main complaints following its excessive use or due to the unusual susceptibility of a patient to it are profuse sweating, marked bodily tremors, and occasionally diarrhea, all of these signs being transitory. Eventually, most patients learn the exact amount which is sufficient to keep their heart rates and rhythms relatively fixed and yet not enough to cause systemic manifestations.

Definite proof that the ephedrine is essential to the maintenance of a sensitized pacemaker is the fact that its repeated withdrawal in patients with fresh disease of the circulation to the auriculoventricular node has invariably resulted in a diminution of the ventricular rate, with the appearance of syncopal attacks.

There is only one contraindication to the use of these drugs that I have encountered in patients with myocardial infarction, auriculoventricular dissociation, and recurrent syncopal attacks. It is in patients with the chronic phases of arterial closure to the node in whom the syncopal attacks are the result of transient periods of ventricular fibrillation and not of standstill of the ventricles.[27] Since similar observations have not as yet been reported in the acute phases of coronary artery closure, there is hardly any likelihood of precipitating ventricular fibrillation with ephedrine sulphate when the ventricles are at a standstill.

Of atropine sulphate, another drug that has been used to stimulate the auriculoventricular pacemaker, there is little to be said. In two patients of this series the injection of atropine sulphate in the early stages of the block was followed by transitory increase in the basic ventricular rate. It must be assumed that the extrinsic nervous mechanism of the heart has an influence over the auriculoventricular node in some patients. Atropine sulphate, however, is used primarily for the pulmonary edema that accompanies a coronary artery lesion frequently, and I have seen only good results following its repeated use for this purpose. In doses of 1/75 of a grain, injected intramuscularly, a lung inundated with edema may be cleared in half an hour.

SUMMARY

1. A study was made of fifteen patients exhibiting the Adams-Stokes syndrome following an acute coronary vessel closure. This group formed one-third of a series of forty-five patients with the Adams-Stokes syndrome seen during a period of four years. There were thirteen males and two females, the youngest being fifty-three years of age and the oldest seventy-one years. In each instance there was evidence of antecedent hypertension, and six patients showed signs of congestive heart failure prior to the present symptoms.

2. Of the fifteen patients, four died within an average of four days, the rhythm returning to normal in two. Seven lived for an average of twenty-six months, with either transient or complete auriculoventricular dissociation alternating during that time. Four are still living with normal sinus rhythm.

3. A permanent drop in the blood pressure after the establishment of a basic rhythm following the acute coronary vessel closure was the most persistent sign of the presence of that lesion.

4. The immediate treatment of such patients consists in the application of warmth to the body to overcome the initial shock and the repeated intramuscular injections of epinephrine hydrochloride until the block is either lifted with a return of normal sinus rhythm, or else a relatively fixed basic ventricular rhythm is established in the presence of auriculoventricular dissociation.

5. The after-care of those patients who still show auriculoventricular dissociation must include the daily administration of ephedrine sulphate to prevent a slowing of the basic ventricular rate. According to the results obtained, neither of these drugs is contraindicated in patients with acute coronary vessel closure in whom the circulation to the auriculoventricular node is involved.

6. Since the auriculoventricular node is in the upper part of the interventricular septum and is supplied by an arterial system in the posterior part of the heart, it may be concluded that patients with complete heart-block and Adams-Stokes syndrome as a result of an acute coronary vessel closure have an infarct in the posterior wall of the left ventricle and the adjacent septum.

7. The electrocardiographic pattern of infarction of the ventricle does not hold true for patients with auriculoventricular dissociation, for, in most of our instances, the electrocardiogram showed intraventricular conduction disturbance.

8. Since, of the fifteen patients with complete heart-block and Adams-Stokes syndrome who survived the acute coronary vessel closure, seven lived an average of twenty-six months; it appears that the prognosis for such patients, as far as longevity is concerned, is not bad.

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COARCTATION OF THE AORTA (ADULT TYPE)

Clinical and Experimental Studies*

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COARCTATION of the aorta is a stricture or stenosis of the aorta. This narrowing is usually found at, or just proximal to, the junction with the ductus arteriosus. Two types, the infantile and the adult varieties as described by Bonnet,[1] are generally recognized. The infantile type, most frequently seen in the newborn, is a diffuse narrowing, or a complete absence of the isthmus (that part of the aorta between the left subclavian artery and the junction with the ductus Botalli). This form is commonly associated with other congenital anomalies and is not compatible with adult life. Infantile coarctation is believed to develop before birth. Adult coarctation is a constriction or obliteration of the aorta at or near the junction of the ductus Botalli with the aorta. Skoda[2] suggested that in the adult type a portion of the tissue peculiar to the ductus extends into the adjacent aortic wall, and, as the atrophy of this tissue occurs, it results in constriction or occlusion of the aorta. The process is a comparatively slow postnatal development and adequate collateral circulation has time to become established. Complete descriptions of the pathology and theories of pathogenesis are available in the papers of Abbott[3-7] and of Blackford.[8]

The symptomatology in coarctation of the aorta varies a great deal. Abbott[6] placed patients in three groups:

1. Those in whom symptoms are absent.

2. Those in whom symptoms are late in developing. These symptoms are flushing of the face, profuse sweating in upper portion of the body, headaches, tinnitus and dizziness, all of which can be associated with the hypertension in the upper extremities, head and neck. At the same time or independently, circulatory insufficiency and intermittent claudication of the lower extremities are often present. In this group sudden rupture of the heart, aorta, or vertebral arteries occurs.

3. Those in whom symptoms are present throughout life. These are usually the symptoms of myocardial failure which often result from secondary chronic valvular disease.

In contrast to these inconstant subjective features of coarctation of the aorta, the physical signs are diagnostic in all the cases prior to terminal complications, as will be discussed below.

CASE REPORT

A nineteen-year-old boy of Austrian parentage entered the medical clinic of the New York Post-Graduate Hospital with a slip of paper detailing the following complaints and symptoms: self-consciousness, nervousness, dreaming every night, tense-

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ness, inability to relax in public, redness of face, especially of the nose, when cold, sweating of hands and armpits, small size of the right side of the chest and arm.

The family history was negative. The patient's two brothers and two sisters were well and free from all physical defects on routine examinations at school. The patient had had the usual childhood diseases. His tonsils were removed at the age of two. His mother stated that he had had rheumatic fever at three. He attended school when six years old and has not been acutely ill since. Another tonsillectomy was performed at ten years of age. When eleven years old he ran a 40-yard race. As a rule he was considered a speedy runner, but on this occasion he was not conscious of the racing interval; at the finish he seemed to awaken and was surprised that he had not won. During moments of excitement, as in fighting, the patient states that his mind would go blank. He remained active in athletics, with no signs or symptoms of cardiac embarrassment, until six years ago when he was told at school that he had heart trouble and high blood pressure. Since then, on the advice of a physician, he has partially curtailed his activities. The patient complained of having been troubled by dreams all his life, and it seemed to him as though his mind was never at rest. He had always been self-conscious and had

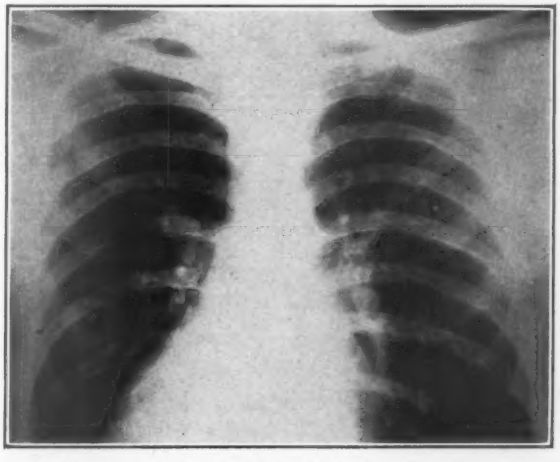

Fig. 1.—X-ray plate of chest showing left-sided hypertrophy of heart, dilatation of the ascending aorta, absence of the aortic knob, and notchings of the inferior border of the ribs.

complained of flushing of his face for eight or nine years. This appeared to be increasing lately. His hands were always clammy, and for the past two or three years his feet have been cold. His nose bled at the slightest trauma.

Physical examination revealed the following: The patient was unusually well-developed, and, although he did not seem nervous, his cheeks were flushed and perspiration trickled from his axillae. His pupils reacted normally to light and accommodation. The arteries of the fundi appeared threadlike, showed a slight degree of tortuosity and streaking, and angiospasm was indicated further by the obliteration of the lumen in the left temporal branch. The veins appeared full. Carotid pulsations in the neck were plainly visible as was also a pulsation at the suprasternal notch. The upper border of a vessel running transversely at the suprasternal notch pulsated strongly. The thyroid gland was not palpable. The precordium appeared to bulge. Expansion was equal and free, and Litten's phenomenon was present, indicating that the diaphragm was not adherent. The lateral thoracic arteries were seen pulsating on both sides, and in a strong oblique light intercostal pulsations were to be observed in the posterior axillary line. The intercostal pulsations and those about the scapulae were readily felt with the finger tips.

A systolic murmur was heard over these vessels. The apex impulse was 10 cm. to the left of the median line in the fifth intercostal space and was distinctly heaving. A loud, rough systolic murmur was heard at the aortic area and was transmitted upward into the neck and through to the back. There was a blowing systolic murmur at the mitral area. The pulse rate was 90 and the rhythm regular. The fingers were blunt but no clubbing was evident. The hands were clammy. Brachial and radial pulsations were marked; femoral pulsations were low and flattened. Pulsations could not be felt in the popliteal, posterior tibial, and dorsalis pedis arteries. The feet were warm. The blood pressure in both arms was equal and ranged from 238/128 on the patient's first visit to 178/90 on subsequent occasions. The popliteal blood pressure was 96/72 at the time of the latter brachial reading, but no popliteal readings could be obtained subsequently upon repeated attempts.

Laboratory Findings.—Blood count showed hemoglobin, 100 per cent; red blood cells, 5,020,000; white blood cells, 8,900. Differential—polymorphonuclears, 64 per cent; lymphocytes, 36 per cent.

Urinalysis showed no abnormal findings. A Wassermann test was negative.

X-ray examination (Fig. 1) showed erosions of lower borders of ribs posteriorly. Increase in total heart area, with transverse diameter 1 cm. above the average normal. The aortic arch appeared receded; the transverse and the descending arch of the aorta could not be found.

Basal metabolic rate was 11 per cent above the average normal.

Renal function tests showed blood urea nitrogen, 10.9 mg. per 100 c.c.; blood nonprotein nitrogen, 27.2 mg. per 100 c.c.; urea ratio, 40 per cent; urea clearance, 106.6 per cent of normal.

Vascular studies are reported and interpreted below.

DISCUSSION

Although there may have been rheumatic fever at three years of age, it is possible that the murmur resulting from the congenital anomaly prompted this diagnosis. While the patient was at school, his condition was not recognized and in a clinic he was told that he was a psychoneurotic. The brachial hypertension in a nineteen-year-old subject with a loud systolic murmur at the base of the heart suggested the existence of coaretation of the aorta. The diminished circulation in the lower extremities and the collateral circulation visible on the chest wall established the diagnosis.

Normal renal function, as indicated by the urea ratio[22] and the urea clearance test,[23] is evidence of adequate circulation throughout the body and to the kidneys.

Since most of the symptoms were referable to increased arterial pressure in the upper part of the body, the effect upon the activity of the thyroid gland was of interest. The basal metabolic rate proved to be normal.

The following studies of the peripheral circulation were done in the vascular clinic under the supervision of Dr. Irving S. Wright.

The surface temperature over the entire body of our patient was within normal limits. On the trunk there was no change indicating a level at which the peripheral circulation was diminished, whereas the extremities showed the normal downward temperature gradient toward the periphery. The temperature of the upper extremities was not con-

sistently higher than that of the lower extremities, despite the difference of blood pressure and major vessel activity. An interesting finding was the definitely higher temperature of the right leg as compared with the left.

The oscillometric curves (Fig. 2) were unusual but were anticipated, in that the curves of the upper extremities showed a much greater oscillometric swing than those of the lower extremities. The curves of the left leg were definitely greater than those of the right leg. This did not correspond with the surface temperature readings as noted above.

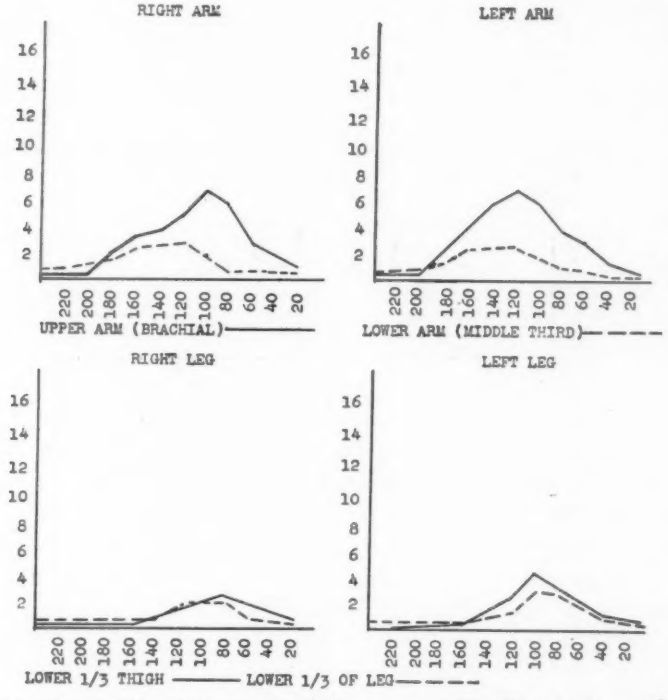

Fig. 2.—Showing oscillometric curves of the upper extremities to be much greater than those of the lower extremities.

A series of hot water immersion tests was performed, according to the technic of Gibbon and Landis.[24] Figures 3, 4, 5 and 6 show that it was possible to produce elevation of the surface temperature of the unimmersed extremities to within normal limits by a variety of combinations of immersed extremities. Figure 7 shows the curve of intravenous temperature of the left anticubital vein, as compared with the surface temperature of the finger tips of the right and left hands, following immersion of the feet in hot water. The intravenous temperature changes accompanied but did not precede the surface temperature changes. The significance of this finding is a moot question at present.

The nail fold capillaries at the finger tips were tortuous, normal in the number active, dilated, and rather bizarre in form. The rate of flow

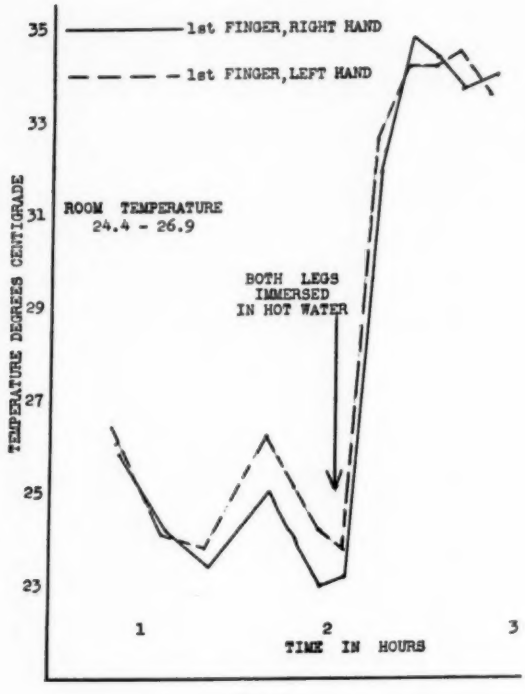
1st FINGER, RIGHT HAND
1st FINGER, LEFT HAND
ROOM TEMPERATURE
24.4 - 26.9
BOTH LEGS
IMMERSED
IN HOT WATER
TEMPERATURE DEGREES CENTIGRADE
35
33
31
29
27
25
23
1
2
3
TIME IN HOURS

Fig. 3.

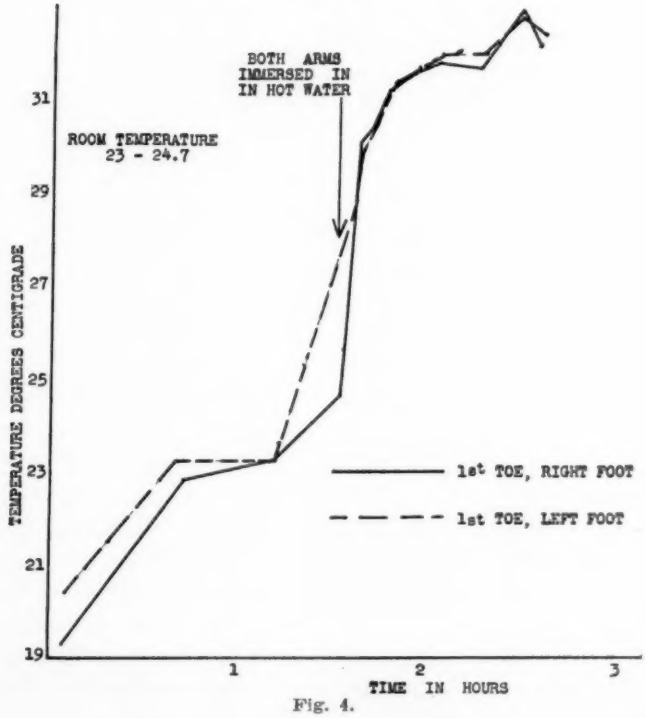
BOTH ARMS
IMMERSED IN
IN HOT WATER
ROOM TEMPERATURE
23 - 24.7
TEMPERATURE DEGREES CENTIGRADE
31
29
27
25
23
21
19
1st TOE, RIGHT FOOT
1st TOE, LEFT FOOT
1
2
3
TIME IN HOURS

Fig. 4.

varied rapidly from fast to slow. The capillaries at the nail folds of the toes were diminished in number, small, constricted, with a slow flow, and were difficult to visualize.

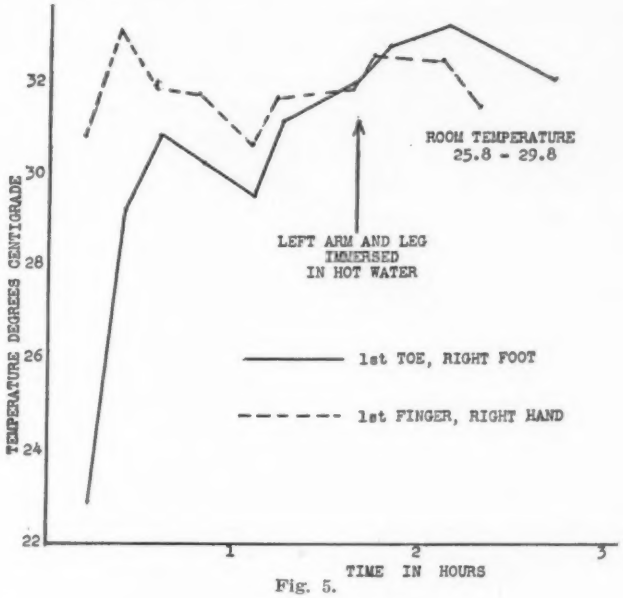

Fig. 5.

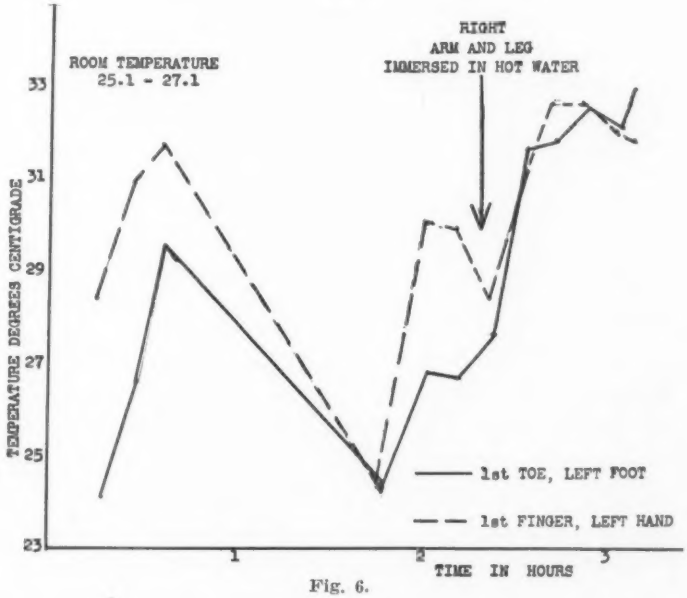

Fig. 6.

The studies of the peripheral circulation demonstrated the remarkable compensatory circulation supplied by the collateral arteries, which permitted normal vasodilatation, as measured by surface temperature readings.

Most cases of coarctation of the aorta remain undiagnosed during life. Abbott[7] reported autopsy findings in 200 cases, 86 per cent of which were overlooked clinically. Blackford[8] found from necropsy reports of approximately 68,300 routine cases, that the incidence of coarctation was about one in 1,550. Paris[9] described the typical pathological findings as early as 1791. Meckel[10] (1827) first observed erosions of the ribs, but his illustration shows these lesions on the superior costal border, while the predominant lesions as generally reported are found on the inferior border of the posterior portion of the ribs. Legrand[11] (1835) made a diagnosis of obstruction of the thoracic aorta based on evidence of col-

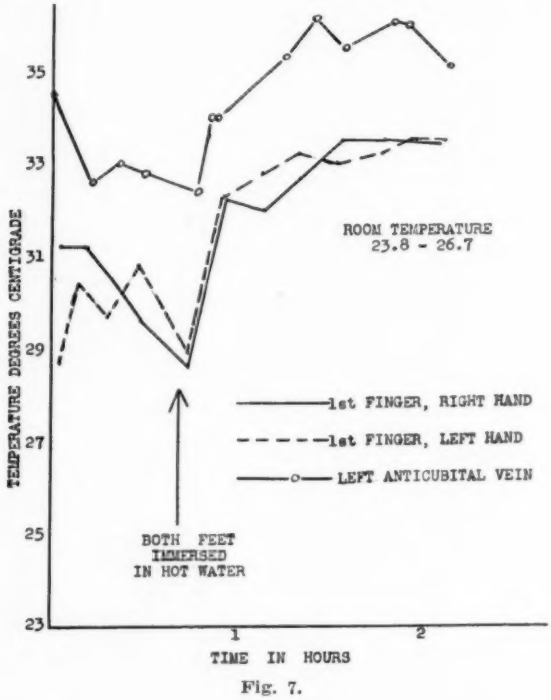

Fig. 7.

lateral circulation over the chest with a diminished femoral pulse. The actual diagnosis of stenosis of the aorta at the ductus was first made in 1848 by Oppolzer, according to Hamernjk.[12] Potain[13] demonstrated hypertension in the upper portion of the body in 1892. Abbott,[3, 4, 5] in 1908 and 1915, called attention to the clinical aspects of coarctation of the aorta and in 1927 supplemented these papers. King[14] (1926) emphasized the important clinical features of stenosis of the aortic isthmus and noted that while only one case was discovered at Johns Hopkins Hospital from 1889 to 1923, three cases were diagnosed in the next three years. In 1928 Abbott and Hamilton[7] made a further extensive report, as did Blackford.[8]

Over one hundred years after Meckel had observed costal erosions as a post-mortem finding, the information was applied clinically by Railsback and Dock[15] (1929). They called attention to the roentgenographic findings of scalloping of the inferior borders of the ribs, absence of the aortic knob, dilatation of the ascending aorta, defect in the aortic arch and left ventricular hypertrophy. Abbott and Hamilton,[7] one year before (1928), had published a roentgenogram showing costal erosions but had failed to comment upon it.

Scheele[16] (1870) made simultaneous tracings of the radial and femoral pulsations. His records show the femoral pulse rising more slowly than the radial, but, according to Lewis,[17] this delay in Scheele's tracing is not measurable. Laubry and Marre[18] (1916) recorded the slow rise of the femoral pulse but observed no delay in the upstroke. Railsback and Dock[15] (1929), by simultaneous electrocardiograms and optical pulse measurements, found the femoral to occur 0.025 sec. after the radial. Blumgart and his associates[19] (1931) stated that normally the femoral pulsation should precede the radial 0.01 to 0.02 sec., but in two cases of coarctation they found the femoral followed the radial by 0.15 sec. and 0.05 sec. Dock[20] (1932) called attention to the difference in quality and time of the radial and femoral pulsation as an easy and reliable diagnostic test. Lewis[17] (1933), investigating six cases of coarctation and five normal subjects, measured the optical pulse and the electrocardiogram simultaneously. He found that normally the femoral upstroke precedes the radial by 0.01 sec., while in coarctation femoral upstroke follows the radial by 0.03 sec.; this delay, he says, is of little clinical significance; however, he finds the lag of the summit of the femoral pulsation is 0.145 sec., and this is easily appreciated with the unaided fingers. Leaman,[21] in the same year, called attention to the diagnostic value of the palpation for a low femoral pulsation in coarctation. Lewis (1933) discussed the subject of aortic coarctation and presented nine cases. Thus each year, as the diagnostic features of this condition have been emphasized and elaborated, there has been a steady increase in the recognition of these cases. In 1934 the *Quarterly Cumulative Index* contained reference to twenty papers dealing with this subject.

The prognosis in this condition is difficult to determine for an individual case but in general may be based upon the compilations of Abbott. Abbott[5] found the average age at death to be thirty-two years, with a range from three years to ninety-two years. The cause of death was as follows: congestive heart failure, 60; sudden heart rupture, 2; rupture of the aorta, 38; cerebral complications, 26; bacterial endarteritis, 14. Although most of Abbott's patients died of cardiac insufficiency, Lewis[17] points out that cases of coarctation are the best evidence that prolonged overwork of the heart in itself does not cause myocardial failure. He observed patients in whom the heart continued

to beat for as long as sixteen years against a systolic pressure of 200 and a diastolic of 100. He states that only 25 per cent of the deaths in coarctation are attributable to congestive heart failure, and in those cases infectious diseases or changes due to advancing age are responsible for the sudden incompetence of the heart. The important fact, as Lewis sees it, is that failure is not inevitable.

SUMMARY

A case of coarctation of the aorta, of the adult type, is reported, together with renal function tests, studies of surface temperature, oscillometric determinations, and capillary studies.

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THE NONFILAMENT LEUCOCYTE COUNT AFTER CORONARY ARTERY OCCLUSION*

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ALTHOUGH when acute coronary occlusion can be recognized clinically the prognosis is serious, it is known that the majority survive the acute attack. The clinical findings that would suggest a less favorable outcome, according to White,[1] are "advanced age, a state of shock, an abrupt and pronounced fall in blood pressure, the prolongation of the severe substernal pain for more than two or three hours, the duration of fever for more than a few days, the presence of high fever (103 to 104° F.), a high leucocytosis—especially if maintained for a week or more, rapid and marked dilatation, gallop rhythm, ventricular paroxysmal tachycardia, heart-block, pulsus alternans, cardiac asthma, congestive failure, and embolic phenomena." The electrocardiogram generally gives confirmatory evidence of the presence of myocardial infarction, although it cannot be relied upon to inform us as to the extent and severity of this pathological change. Certain blood studies have been carried out in the hope of yielding useful information on this point. Knowing that absorption from necrotic processes causes lowering of the red cell sedimentation time, Rabinowitz and his coworkers[2] became interested in this reaction following acute coronary occlusion. In 10 such cases they found uniformly an increase in the rate, the change being most marked on the third to fifth day, and persisting longer than fever or leucocytosis. Burak[3] reports a similar study on six patients. Steinberg[4, 5] followed the nonprotein nitrogen level of the blood in cases after coronary occlusion and reported that a filtrate nitrogen, remaining high or continuing to rise, was of serious significance.

Many previous articles have mentioned the characteristic increase in the total leucocyte count. White[1] states that the grade and duration of leucocytosis is a useful clue to the size of the infarct and hence to the prognosis. Libman and Sacks[6] state that leucocytosis is the most frequent significant feature of the condition. Of a series of 74 patients reported by Levine,[7] only 4 had a total white blood cell count of less than 10,000. All of the 14 patients reported by Coffen and Rush[8] had leucocytosis after acute coronary occlusion, and all but 3 of the 19 reported by Wearn.[9] Hamman[10] states that the average leucocyte count in this condition is 12,000 to 15,000. Rarely is the count more than 30,000. Levine and Brown[11] had one such patient with a 34,500 count, and Hines[12] had one in which the total count exceeded 100,000 for a

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period of twelve days. In our own entire series of coronary occlusion cases 35,700 has been the maximum count. This patient died, and autopsy showed extensive infarction of the myocardium. It is usually assumed that such marked increases in the total white cell count indicate extensive acute myocardial pathological change, and therefore a more serious prognosis, and in the main this is borne out by the outcome in such cases.

In applying the filament-nonfilament count in several patients after coronary occlusion, we were struck with the fact that there was a "left shift" present which was frequently quite pronounced. It was then decided to follow several such consecutive cases, doing frequent simul-

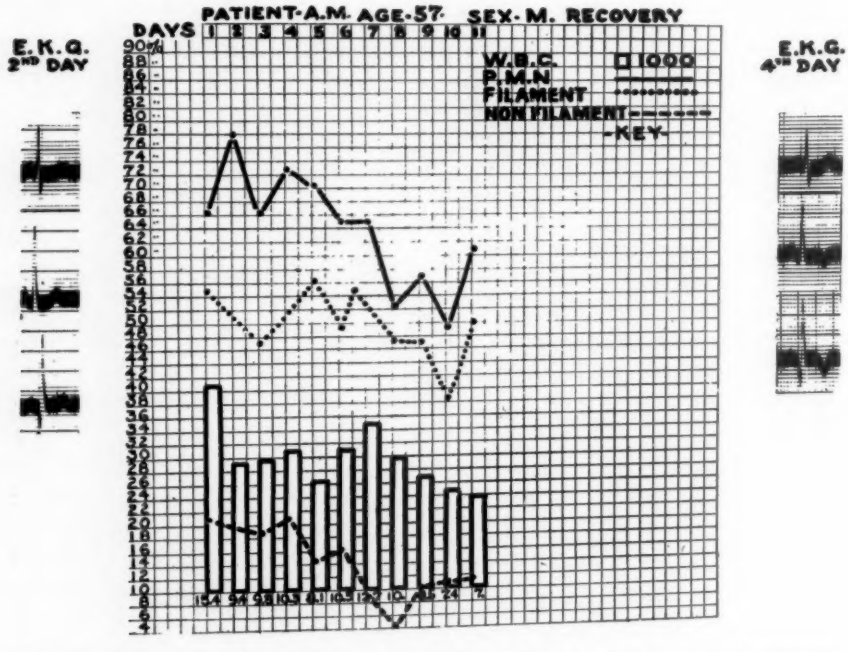

Fig. 1.—An example of a rather mild and favorable case of coronary thrombosis. The electrocardiograms are offered corroborating the diagnosis. The nonfilament percentage curve is relatively low and a wide separation is seen between it and the filamented cell curve.

taneous total leucocyte counts and differential counts according to the usual type, as well as filament-nonfilament counts, plotting the results graphically. This procedure was carried out in fifteen cases of coronary artery occlusion, and a total of 189 such counts were made. The differential percentages were obtained by counting 200 cells on each slide. The counts and slides were usually obtained between 9:00 and 11:00 A.M., and only from hospitalized patients. Curves were plotted for the individual patients, and subsequently, composite graphs were made of the eleven who recovered and the four who died. In these charts are shown the total leucocyte count, the polymorphonuclear neutrophile percentage,

the filament and nonfilament counts and, in one of the combined graphs, the eosinophile percentages as well. It was hoped that in following these counts serially some information might be encountered which could assist the accuracy of prognosis in the acute attack of coronary thrombosis. It is realized that comparing averages of a series of four fatal cases to those obtained from a series of eleven recovered cases is open to some criticism. However, as in any series of acute coronary occlusion, the nonfatal cases will exceed the fatal ones during the first several weeks; such a disproportion will always be found if the cases are consecutive.

THE TOTAL LEUCOCYTE COUNT

In both the recovered and fatal cases, the total white cell count was highest on the second and third day after occlusion, averaging about

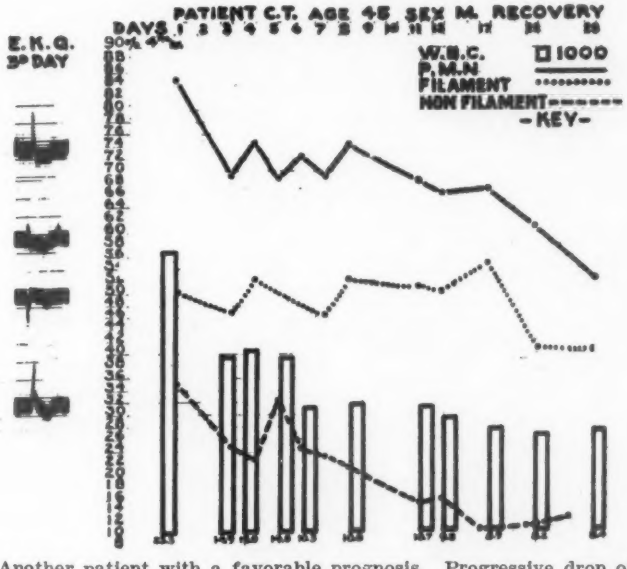

Fig. 2.—Another patient with a favorable prognosis. Progressive drop of the nonfilament count after the fifth day. Wide separation between the filament and nonfilament curves. Electrocardiogram taken on third day shows characteristic changes of coronary occlusion.

2,000 higher in those patients who died. It was 17,700 in the fatal, 15,900 in the recovered group. A slight increase was maintained throughout in the four fatal cases. It may also be noted that an average leucocytosis of about 10,000 continued, even in the recovered cases, to as late as the nineteenth day.

THE POLYMORPHONUCLEAR PERCENTAGE

This percentage was at its maximum during the first few days, and thereafter it fell progressively in both groups. After the eighth day in the recovered group it continued to fall slightly, whereas in those patients who died it remained above 70 per cent.

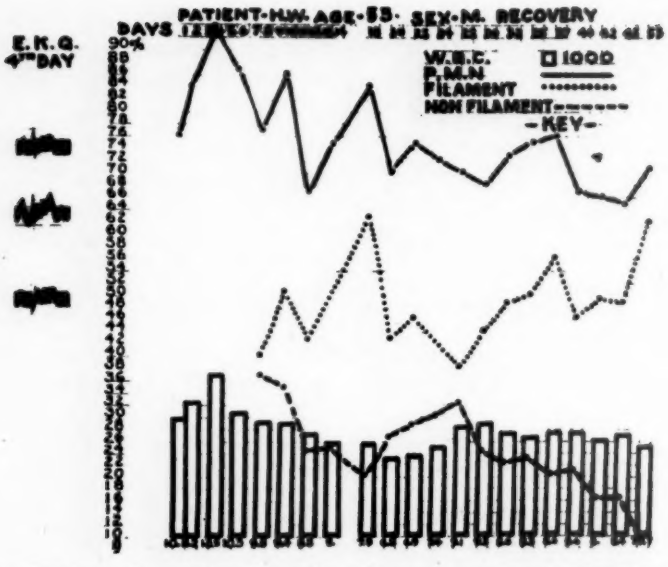

Fig. 3.—A patient who recovered in spite of a severe coronary obstruction. Unfortunately the nonfilament counts were not begun until the eighth day. Nonfilament percentage curve and filament curve are almost together on eighth day, and the nonfilament curve rises to a secondary peak of 32 per cent on the twenty-eighth day and afterward falls progressively to normal on the fifty-third day. Characteristic electrocardiogram on fourth day.

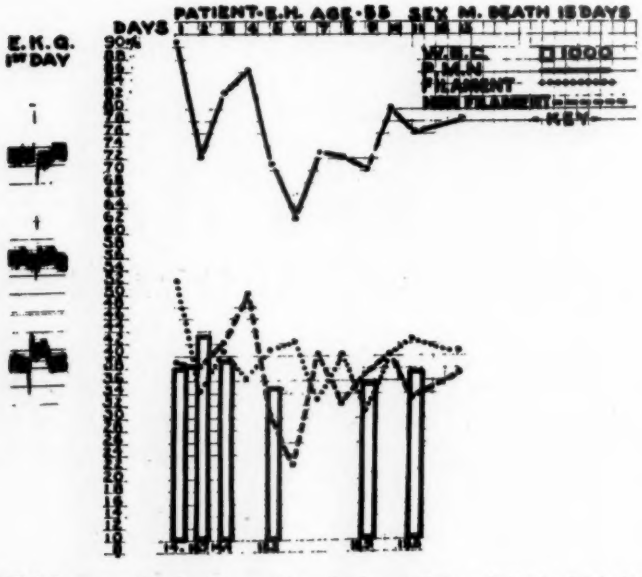

Fig. 4.—Fatal case with death on fifteenth day. Note relatively high initial polymorphonuclear count and peak of nonfilamented percentage as high as 50 per cent on the fourth day. The filament curve repeatedly crosses the nonfilament curve after the fourth day. Typical electrocardiogram.

THE NONFILAMENT COUNT

The neutrophilic leucocytes were recorded as nonfilamented and filamented cells. Farley, St. Clair, and Reisinger[13] suggested this simplification. Their average percentage of one lobed cells in ten normal persons was 9.2 per cent, with 16 per cent stated to be the upper limit of normal. Needles[14] in an equal series obtained 8.45 per cent as the average normal and used 16 per cent as the upper limit of normal. Schilling[15] with normal total white blood cell limits at 5,000 to 8,000 reports 3 to 6 per cent as the normal number of nonfilamented cells.

In our fifteen patients followed in this manner, the nonfilament or one lobed cells were uniformly elevated above the upper limit of normal (16 per cent). It was noted in averaging the recovered and fatal cases that this count offered a more striking contrast than was presented by either the total white cell count or the polymorphonuclear percentage. In both the recovered and fatal group, the count commenced relatively high on the first day after occlusion and had a rather sharp drop the second day, rising again to a maximum on the fourth day. In the recovering patients, after the eighth day it fell gradually to a normal level on the sixteenth day. In the four patients who died, the average nonfilament percentage was almost double that in the recovering patients and, after the eighth day, instead of declining, the curve steadily rose as high as 37 per cent on the twelfth day. This nonfilament count in the early stage of infarction was often proportional to the total white cell count, except for the sharp drop on the second day. Later on, however, in the recovered group it fell to normal even when the total white cell count remained around 10,000.

EOSINOPHILE PERCENTAGE

In certain acute infections, the reappearance of eosinophiles and their increasing percentage are thought to be some of the earlier evidences of subsidence of the infection and the onset of recovery. A moderately striking contrast is offered in the comparison of the average eosinophile percentage curve of the fatal to that of the recovering patients after coronary occlusion. In the fatal group, no eosinophiles were found before the fifth day after occlusion. The curve then rose gradually to a maximum of 1.7 per cent eosinophiles on the tenth day and dropped abruptly thereafter to zero on the twelfth day. In the recovering patients, a 0.4 per cent eosinophile average was present the first day after occlusion, and the curve increased progressively up to 3.6 per cent on the fifteenth day.

THE FILAMENT COUNT

Nothing has been said up to this point regarding the graph of the filamented neutrophiles since after all this percentage is complementary to the nonfilamented curve and simply indicates the proportion of more

mature neutrophiles to the total leucocyte count. However, a review of all our fifteen individual cases, as well as of the combined graphs, reveals some points of interest. First, in three out of the four fatal cases the nonfilament curve crossed the filamented graph or was repeatedly intermingled with it, and in each of the three charts intersection of these curves occurred as late as the sixth day and after. Of the eleven recovered cases the filament and nonfilament curves intersected in three cases on the fourth day and in one on the fifth. After this day, a wide separation of the two curves was present in all the recovering patients. Similarly, a comparison of the combination graphs of the patients who died and those who recovered reveals that in the fatal group the filament and nonfilament curves are separated by a relatively

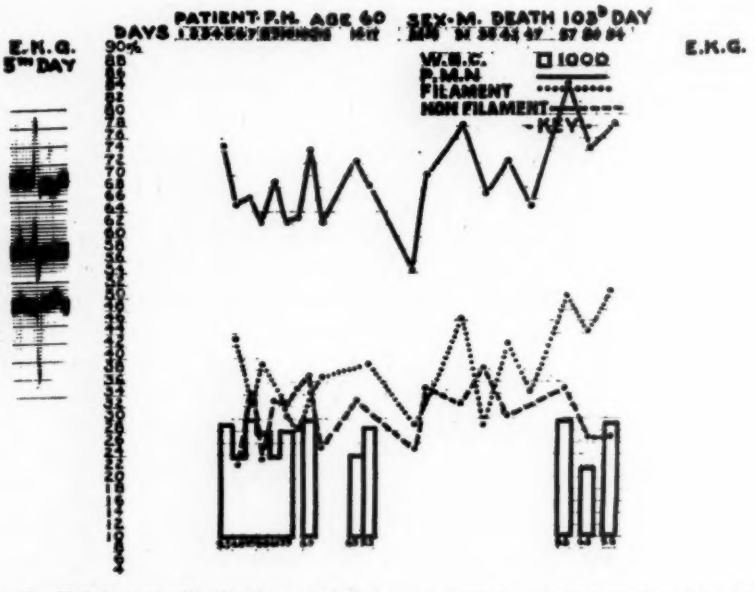

Fig. 5.—Fatal case with death on 103rd day. Prognosis seemed unfavorable during observation. Note nonfilament curve persisting above 30 per cent and repeatedly intersecting the filament curve after the fifth day.

slight space, are quite close together on the fourth day, and meet on the seventh and eleventh days. The "recovered" group averages, however, maintain a wide separation between the filament and nonfilament percentage curves throughout a nineteen day period.

Many conditions other than infections produce leucocytosis, such as the taking of food, exercise, and pregnancy. Walton[16] reports a consistent elevation accompanying fractures. Pepper[17] cites cerebral hemorrhage with 16,600 leucocytes and paroxysmal tachycardia with 17,100. Patients with congestive cardiac failure usually show a slight leucocytosis.

The peculiar conformation of the nonfilament curve in both the recovered and fatal cases in the first four days after acute coronary oc-

clusion—showing a high figure the first day, a sharp drop the second, followed by a progressive rise to a maximum on the fourth day—would suggest a need for explanation. Libman and Sacks[6] report leucocytosis

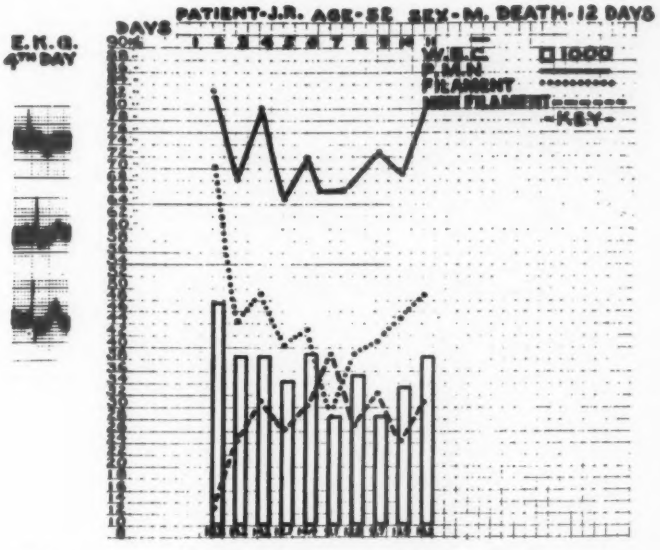

Fig. 6.—Fatal case. After the fourth day the nonfilament curve remains above 30 per cent and is intersected by the filament curve on the seventh day. Characteristic electrocardiographic changes.

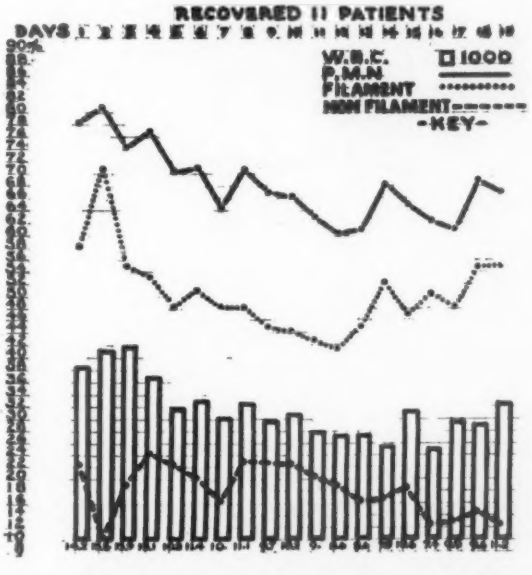

Fig. 7.—Graph showing average counts on the eleven patients who recovered. Note wide separation of filament and nonfilament curves. Moderate elevation of nonfilamented percentage to 22 on first day and sharp drop to a normal level on second day, then progressive rise to maximum of 24 on fourth day with gradual decline afterward. The polymorphonuclear percentage falls gradually from the first day.

occurring within one and one-half hours after acute coronary occlusion. Fraenckel and Hochstetter[18] observed leucocytosis in partial asphyxiation of rabbits, the maximum being within five hours. Holst[19] believes that the early leucocytosis in coronary occlusion is due to an excess of carbon dioxide. Reveno[20] notes 14 per cent nonfilamented leucocytes in congestive cardiac failure. Fanelli,[21] likewise, found a usual but inconstant slight increase in the nonfilament percentage. He suggests this may be due to two factors: the increased carbon dioxide percentage stimulating the production of young forms and the lessened oxygen content preventing the usual maturation to older forms. The initial high nonfilament percentage in our series of patients may be due to shock

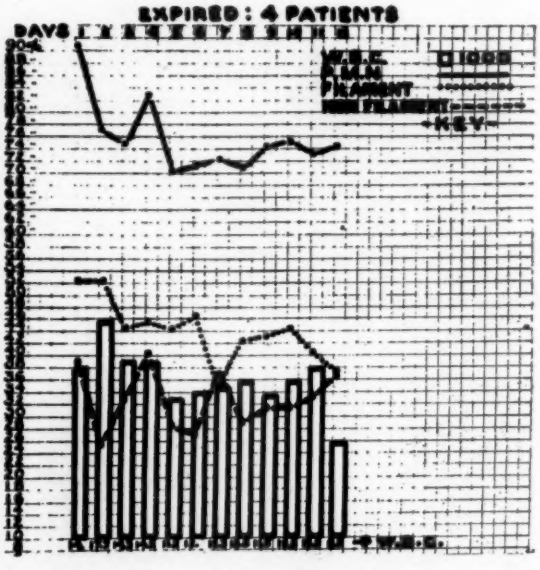

Fig. 8.—Graph showing average counts in four fatal cases. The polymorphonuclear percentage is higher than in Fig. 7. The nonfilament count persists at a high level, above 30 per cent intersecting the filament curve on the seventh day and again meeting it on the twelfth day. Note the nonfilament rise the first day to 38 per cent with a drop the second day to 24 per cent, the secondary peak of 40 per cent on the fourth day.

and excess carbon dioxide, while the sharp drop on the second day may be explained by a recession of this reaction and the absence at this point of the complete development of the myocardial infarction.

It is well known that after obstruction of arterial supply in any location, infarction takes time to develop and reach its maximum extent; furthermore, the speed of development is not always the same and may depend on many variable factors. Groyzel and his associates[22] were not able to demonstrate any anatomical change in dogs earlier than ten hours after closing a coronary artery. Later on there developed edema, hemorrhage, and slight polymorphonuclear infiltration. When a myocardial infarct is large, it seems obvious that there will be a greater

opportunity for the absorption of toxic substances from the necrotic area, that a longer time will be required for repair and that a greater probability will exist for a fatal outcome during the early period after the coronary artery occlusion.

We believe that the curves encountered in the leucocyte and differential counts are directly related in the main to the evolution of the myocardial infarct. The combination of nonfilament count and eosinophile percentage behaves in this condition in the same way that it does in certain acute infections, i.e., early in either condition: when absorption from either infection or necrosis is marked, the nonfilament count is

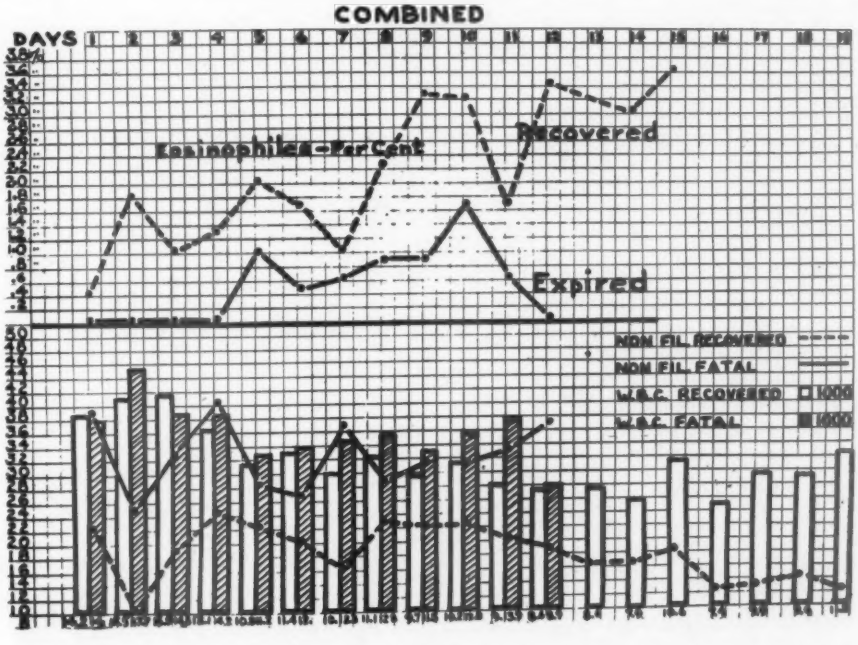

Fig. 9.—The upper half of this chart depicts the average eosinophile percentages in the recovered and fatal cases. Note the absence of eosinophiles in the fatal group before the fifth day, also the progressive upward trend in the recovering cases as high as 3.6 per cent on the fifteenth day. The lower chart compares the total leucocyte counts in the fatal and nonfatal cases, also the nonfilament percentage curves. The total white count maintains a slightly higher level in the fatal group. The nonfilament percentage is nearly twice as high in the fatal cases as in the recovered.

relatively high and the eosinophiles low or absent; while with the onset of recovery, the reverse is true, and the eosinophile curve rises as the nonfilament curve drops toward normal. In our cases, this change was most pronounced in the recovering or nonfatal cases about the eighth to tenth day.

SUMMARY

The total white cell count is increased after coronary artery occlusion, averaging from 13,000 to 18,000 in the first four days. In a fatal case

one count as high as 35,700 was encountered. The average leucocyte count has been found to be slightly higher in the patients who died than in those who recovered.

The polymorphonuclear neutrophile percentage is above normal, being somewhat higher in the fatal group than in the recovered group.

The average nonfilament curve was found to be almost twice as high in the fatal cases of coronary occlusion as in the recovering group, and in the combined graph of fatal cases the nonfilament average was as high as the filamented average on the seventh and eleventh days; while in the recovering group, although a few cases showed an intersection of these two curves on the fourth day, in the main there was a wide separation between them.

The eosinophiles were absent in the four fatal cases up to the fifth day, the curve slowly rising to 1.6 per cent on the tenth day, and then falling to zero on the twelfth day. The recovering group showed an earlier appearance of eosinophiles and a higher and more progressive rise to 3.6 per cent on the fifteenth day.

CONCLUSIONS

An unusually high total leucocyte count early after occlusion is thought to be of serious significance.

A nonfilament percentage curve persisting above 30 per cent beyond the fourth day after coronary occlusion would suggest a large area of infarction and hence an unfavorable prognosis.

An absence of eosinophiles or an eosinophile curve not rising above 1.5 per cent in the first ten days appears to be rather unfavorable.

A nonfilament percentage curve ranging below 25 per cent, and an eosinophile percentage appearing early and rising above 3 per cent would suggest a less extensive area of myocardial infarction and a greater probability of recovery.

The daily plotting of graphs of the differential and filament-nonfilament counts after acute coronary occlusion gives information of distinct value in estimating the prognosis and this information is superior to that obtainable from the total leucocyte count alone.

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AN ANALYSIS OF THE RELATIONS OF THE CORONARY CONSTRICTOR AND DILATOR NERVES IN THE CERVICAL VAGOSYMPATHETIC OF THE DOG* †

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COLUMBIA, MO.

THE original demonstration of coronary vasoconstriction was based on the effects of stimulating the cervical vagus (or vagosympathetic) in the cat. Upon stimulating this pathway Porter[1] in 1896 observed a reduction in the number of drops in the outflow from opened coronary veins. He postulated efferent vasoconstrictor neurones in the vagus trunk and their origin from the medulla oblongata.

The somatic vasoconstrictor nerves arise from the central nervous system in the thoracolumbar cord and course through the anterior roots of the spinal nerves, via the white rami communicantes to the sympathetic chain ganglia and by devious and often quite indirect paths to their peripheral distribution. The vagus is a cranial parasympathetic nerve; the presence of vasoconstrictor neurones to the coronaries via the vagus forms an unexpected exception to the general course of vasoconstrictor distribution to other regions of the body.

In an earlier paper[2] evidence is given showing that the reaction of the coronary blood vessels to cervical vagosympathetic stimulation in the dog is unpredictable in that it is sometimes constrictor and sometimes dilator in effect. Close physiological and morphological association between the paths of the efferent dilator and the constrictor neurones to the body in general suggest a similar common central origin for the neurones distributed to the coronaries. A plausible hypothesis is that the neurones of each of these pathways may arise in the thoracic cord, and the postganglionic neurones of each be distributed from the sympathetic ganglia, even as high in the chain as from the superior cervical ganglion. The reactions reported in the literature to tests in the normal animal applied to the midcervical region of the vagosympathetic trunk are about as readily explained on the assumption of a thoracic origin as on a vagal origin of the coronary constrictors.

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*This report is based on the study of two series of dogs. The writer is indebted to the Institute for Medical Research of the Mayo Foundation for the facilities of the institute in the preparation and study of the first group of these animals.

I am deeply grateful for the assistance of the director, Dr. Frank C. Mann, and of Dr. Hiram E. Essex and the laboratory staff. Dr. Mann kindly operated upon the dogs, and Dr. Essex and the laboratory staff gave untiring support during their physiological testing. The second series was operated upon and tested in the laboratories of the University of Missouri. Grateful acknowledgment is extended to Dr. Robert W. Siddle and Dr. James A. Atkins and the junior members of the staff for aid both in the surgery and the physiological testing of this series.

†A research grant from the National Research Council has covered part of the expense of calculating and tabulating the voluminous data from these tests. Sincere appreciation of this scientific aid is hereby recorded.

A definitive test devised to establish conclusively the true origin and pathway of distribution of the coronary vasoconstrictor neurones is the experimental task we have undertaken in the present research.

ELIMINATION OF THE CORONARY CONSTRICTOR NEURONES BY DEGENERATION OF THE VAGUS TRUNK

The only conclusive procedure to prove the hypothesis of vagal origin is the complete removal of vagal neurones from the common vagosympathetic pathways. This can be accomplished by the process of surgical interference and physiological degeneration, followed by analytical experiments applied to the nerve trunks after the degenerative loss of the efferent group of vagal neurones.

We have sectioned the vagus between the ganglion nodosum and the exit of the vagus roots from the jugular foramen. This is the operation used by Morgan and Goland,[3] and by Heinbecker and O'Leary.[4] Vagotomy was carried out aseptically on dogs under ether. Unilateral transsections were done central to the ganglion nodosum, leaving one vagus intact for later experimental comparisons. The superior cervical ganglion of the side operated upon was also freed at the time of the vagotomy and the two closely bound ganglia transposed out of their normal positions as a drastic check on the cutting of all rootlets.

Animals were tested for evidence of nerve control of the coronary flow after varying operative intervals of from 8 to 188 days. The right vagus was usually sectioned. Dogs survive this unilateral operation well and are in good physical condition for the final functional tests.

METHODS OF TESTING CORONARY NERVE CONTROL AFTER DEGENERATION OF THE VAGUS

Coronary control after degeneration of the vagus was tested by stimulation of the peripheral cervical vagosympathetic, or the cardiac nerves in the thorax, and recording the reactions in terms of variations in the rate of flow of blood from the coronary sinus. The experimental tests were done with open chest under ether anesthesia, with heparin to prevent clotting of blood. The arterial pressure was equalized and recorded as described in a previous paper.[2]

The experimental sequence was as follows: First, the unoperated cervical vagosympathetic was stimulated for evidence of the presence of normal inhibitory vagus neurones. A positive reaction of inhibition was accepted as proof that the degenerated vagus originally contained a similar quota of active inhibitory neurones.

The degenerated vagus was then tested for cardiac inhibitory fibers. The failure of inhibitory response is the most sensitive physiological proof of the completeness of degeneration of efferent vagal neurones. The crucial experiment for which these steps are purely preliminary is

Fig. 1.—Dog 3. Test 1: Presents the usual vascular responses to stimulation of the normal vagosympathetic of the dog. The blood pressure is controlled, hence shows only immediate reaction changes. The coronary dilation in the after-period is largely reflex.

Test 2: Gives the responses of the right vagosympathetic after the vagus was cut above the ganglion nodosum and the vagal neurones had degenerated. It is assumed that the cardiac acceleration and coronary dilation of 23 per cent are due to the stimulation of cervical sympathetic neurones which are not now opposed by vagal constrictor and inhibitor neurones. The experiment should be compared with that of Fig. 2. Time in 5-second intervals. Stimulus from a Harvard inductorium supplied by one dry cell. (Reduced to 46 per cent of original size.)

the test for coronary constriction. It seemed to the author that negative inhibitory evidence would strengthen the value of the method of degeneration in the study of the nerve control of coronary constriction.

PROTOCOL I

Dog 3. Test 1: Stimulating the left vagosympathetic above inferior cervical ganglion, 8 cm.

TIME	BLOOD PRESSURE	PER CENT CHANGE	HEART RATE	PER CENT CHANGE	CORONARY FLOW	PER CENT CHANGE
10″ before	87.0		126		36	
4″ after	31.0		Heart Inh. 4 sec.		Flow stopped 3 sec.	
10″ after	79.0	−9	144	14	32	−11
20″ after	85.0	−2	126	0	36	0
30″ after	89.0	2	126	0	38	6
45″ after	91.0	4	132	5	42	17
60″ after	94.0	8	132	5	42	17
80″ after	93.0	7	126	0	41	14
90″ after	91.0	4	126	0	39	8
Test 2: Stimulating right degenerated vagosympathetic above the inferior cervical ganglion, 8 cm.						
10″ before	89.0		126		39	
10″ after	100.0	12	144	14	48	23
20″ after	93.5	5	129	2	44	13
30″ after	93.6	5	126	0	42	8
45″ after	93.0	5	126	0	42	8
60″ after	91.5	3	126	0	41	5
90″ after	93.0	5	126	0	42	8

CORONARY RESPONSE TO CERVICAL VAGOSYMPATHETIC STIMULATION AFTER VAGAL DEGENERATION

Complete loss of coronary constriction was the typical response to stimulation of the operated cervical vagus. Inhibitory control of the heart rate was also lost in every degenerated nerve examined, always present in the normal unoperated vagus. The data on the heart rate alone support the efficiency of the degeneration method in application to the problem of coronary control. The complete disappearance of coronary constriction after the vagus was cut and allowed to degenerate is conclusive proof that the constrictor fibers are true efferent vagal neurones. We have pursued the problem by further analytical tests in search of other pathways. All such experiments have been relatively, but not exclusively, negative.

Dogs vary greatly among themselves in the mass and course of their cardiac neuronal architecture. This fact accounts in some degree for certain seemingly contradictory experimental data. In certain animals, Animal 7, Test 6, Fig. 2, there was no visible response of any kind to cervical vagosympathetic stimulation in the degenerated nerve. This is in exact contrast to Animal 3, Test 2, Fig. 1, in which stimulation of the degenerated vagus (cervical vagosympathetic) yielded both coronary dilation and cardiac acceleration. The failure of coronary responses in the degenerated vagus of Animal 7 is an example of individual variation. This particular dog had lost its coronary constrictor and

cardiac inhibitory neurones by degeneration and never did possess cervical sympathetic neurones of either dilator or accelerator type. In Animal 3 both groups of neurones were present in the corresponding region of the vagosympathetic trunk. The possibility of coronary dilator neurones in the operated trunk must be eliminated from the cervical field before final proof of complete degeneration of coronary constrictor nerves can be made.

PROTOCOL II

Dog. 7.—Wt. 8.8. kg. Tested 107 days after vagosection above the ganglion nodosum. Heparin, 50 mg. per kilogram. Donor blood used. Blood pressure uniform.

Test 6: Stimulating the right vagosympathetic, 5 cm. above the inferior cervical ganglion, 6 cm.

TIME	BLOOD PRESSURE	PER CENT CHANGE	HEART RATE	PER CENT CHANGE	CORONARY FLOW	PER CENT CHANGE
10″ before	75.4		156		45.9	
30″ after	70.5	– 7	156	0	46.8	2
60″ after	68.7	– 9	156	0	45.5	–1
90″ after	66.4	–12	156	0	46.4	1
120″ after	67.1	–11	156	0	45.3	–1
150″ after	67.1	–11	156	0	44.5	–3
180″ after	68.7	– 9	156	0	44.8	–2
Test 7: Stimulating the right inferior cervical ganglion, 6 cm.						
15″ before	68.7		156		44.8	
15″ after	74.5	8	252	62	75.4	68
30″ after	66.1	–4	192	23	65.0	45
45″ after	64.1	–7	174	12	51.6	13
60″ after	64.1	–7	168	8	48.5	8
75″ after	66.0	–3	168	8	45.2	1
90″ after	66.6	–3	168	8	44.9	0
120″ after	68.4	0	168	8	44.1	–2
150″ after	67.5	–2	168	8	43.0	–4
210″ after	73.0	6	162	4	41.3	–6

Nicotine was injected into the inferior cervical ganglion in each of two operated dogs in order to remove the masking effects of sympathetic reactions on any possible undegenerated inhibitory or constrictor neurones. Upon stimulating the cervical vagosympathetic trunk one animal yielded no variations from the previous dilator reactions. The other animal gave a mild degree of coronary constriction, Dog. 4, Tests 26 and 27. The tests demonstrate that a mild degree of coronary constriction may become evident only when the masking dilator reactions are removed.

The amount of coronary constriction observed in Animal 4 was little more pronounced than the allowable factor of error in measurement, and yet too great to discard. On the whole, we give weight to this evidence as indicating the occasional presence of a comparatively few neurones of the efferent coronary constrictor type lying in the ganglion nodosum or adjacent vagus trunk. The assumption of a slight degree of embryonic dispersion by centrifugal migration of the neuroblasts of the neural crest which gives rise to the coronary constrictor center is indicated.

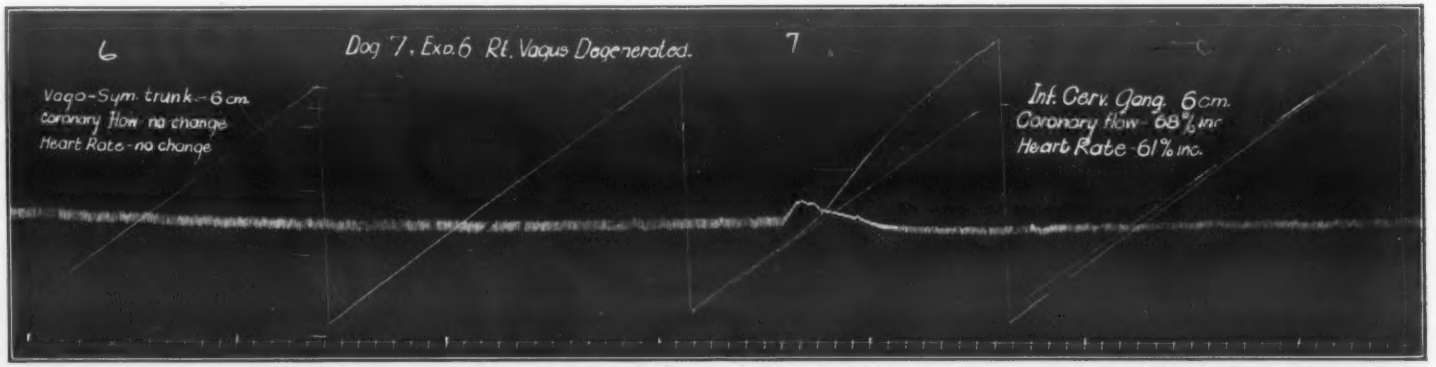

Fig. 2.—Dog 7. Test 6: Shows complete absence of any response to stimulation of the cervical vagosympathetic trunk, 6 cm. The conclusion is drawn that neither coronary dilator nor coronary constrictor fibers are present in the cervical trunk of this particular animal. It is to be compared with Fig. 1, Test 2.

Test 7: When the electrodes were applied to the inferior cervical ganglion, with the same strength, 6 cm., a voluminous coronary dilation promptly occurred. The coronary flow increased 68 per cent. There is a corresponding increase in cardiac rate, but the relationship is not causal. (Reduced to 58 per cent.)

EVIDENCE OF CORONARY DILATOR NEURONES IN THE CERVICAL SYMPATHETIC AFTER DEGENERATION OF THE VAGUS

Degeneration of the coronary constrictor and of the cardiac inhibitor neurones prepares a simplified structure on which to search for the presence of antagonistic coronary dilator as well as cardiac accelerator pathways in the cervical sympathetic trunk. Table II of an earlier paper[2] presents evidence for the presence of neurones of the dilator group obtained from tests complicated by the simultaneous reactions of coronary constrictor neurones in the cervical vagosympathetic trunks of normal unoperated animals.

TABLE I

CERVICAL VAGOSYMPATHETIC STIMULATION AFTER DEGENERATION OF THE VAGUS

ANIMAL AND TEST NO.	STRENGTH OF STIM. IN COIL POSITION (CM.)	TIME FROM BEGINNING OF STIM. (SEC.)	PER CENT OF CHANGE			POINT OF STIMULATION OF VAGOSYMPATHETIC
			BLOOD PRESSURE	HEART RATE	CORONARY FLOW	
1— 6	6	40	–1	2	12	Nodosal and sup. cerv. gang.
1— 9	6	45	–1	0	9	Nodosal and sup. cerv. gang.
2—16	6	30	0	2	– 4	Nodosal and sup. cerv. gang.
		90	1	0	– 9	
6—12	4	30	1	0	–10	Nodosal and sup. cerv. gang.
5— 8	4	35	–1	–2	– 9	Just below nodosal and sup. cerv. gang.
4—14	4	15	5	25	18	Midneck
		30	–3	6	1	
5— 6	6	15	–1	6	14	Midneck
6— 7	6	15	–1	0	30	Midneck
		30	–1	–4	44	
		90	–6	–7	63	
6—22	6	20	–1	2	–4	Midneck
		40	0	5	8	
10—12	4	20	0	31	22	Midneck
5—31	4	20	1	22	18	3 cm. above inf. cerv. gang.
		30	0	7	1	
		120	–3	0	26	
7— 3	8	30	2	–4	2	3 cm. above inf. cerv. gang.
		120	–2	–4	10	
9—49	4	30	1	0	–2	3 cm. above inf. cerv. gang.
		60	1	0	–2	
3— 2	8	10	12	14	23	2.5 cm. above inf. cerv. gang.
		30	5	0	8	
		60	3	0	5	
5—39	4	25	9	46	19	1.5 cm. above inf. cerv. gang.
		60	0	2	–4	

Stimulation of the vagosympathetic between the superior and inferior cervical ganglia after degeneration of the vagus generally produces coronary dilation (Fig. 1, Test 2). The reaction is more profound when the stimulus is applied to the trunk near the inferior cervical ganglion. In fact, as already stated, it sometimes fails at the middle of the trunk or toward the superior cervical ganglion (Fig. 2, Test 6).

Complete analysis of the problem presented is more difficult than at first appears. The location of the postganglionic cells of the few coro-

nary dilator fibers which form a pathway above the inferior cervical ganglion has been assumed to be in the superior cervical ganglion. The bundles of postganglionic fibers run down the cervical vagosympathetic toward the heart and should be available for stimulation and give approximately the same volume of reaction wherever stimulated along their cervical course. This hypothesis did not stand the test of experimental proof in two particulars: First, the coronary dilator reaction sometimes failed altogether in the midcervical trunk, and second, the volume of coronary dilation was greater when the stimulus was applied near the inferior cervical ganglion.

Simultaneous stimulation of the ganglion nodosum and the superior cervical sympathetic ganglion, or of the cervical vagosympathetic in the upper neck area of the operated vagus, produced only slight coronary effects. Sometimes there is mild constriction, as in Dog 2, Test 16, or coronary dilation, as in Dog 1, Tests 6 and 9, or no effects at all, as in Dog 7, Test 6 (Fig. 2). Such seemingly contradictory data are to be anticipated in consideration of the possibility of complete absence of, or variation in numbers of, superior cervical coronary dilator neurones, in combination with an equally variable number of undegenerated coronary constrictor neurones outside the medullary center.

The coronary dilation in response to cervical stimulation may range from 0 to 30 per cent if the vagus is degenerated, depending upon the location of the point stimulated. If the isolated superior cervical sympathetic ganglion is stimulated, the coronary dilation is not so massive and sometimes fails, a fact which argues for few, and in some animals no, neurones in the superior cervical reflex arc. This explains Fig. 2, Test 6, in that this animal had no cervical dilator and no accelerator neurones, and no coronary constrictor neurones distal to the point of vagosection, hence its reactions were quite negative.

EVIDENCE OF DILATOR REACTION BY WAY OF A MIDDLE CERVICAL MICROGANGLION AFTER DEGENERATION OF THE VAGUS

If the point of stimulation is moved along the cervical vagosympathetic toward the inferior cervical ganglion, the amount of dilation becomes greater. In midcervical stimulation of Dogs 4 and 5 coronary dilation was slight, though in Dog 6, Test 7, it was greater. These are examples of mass variation of each of these two groups of cervical nerves among individual animals. The reaction of each group is small, but one's inability to determine to what extent each is present is sufficient to confuse the judgment upon the total significance of the data from the normal animal.

If the electrodes are placed on the cervical trunk within 2 cm. of the inferior cervical ganglion, there is a stronger coronary dilator reaction. Extrapolar stimulation may be ruled out. The observed responses suggest ganglionic synapses in the vagus trunk at this region.

There is gross anatomical evidence of a middle cervical ganglion in about 1 per cent of the dogs that come to autopsy. The greater dilation upon stimulation just above the inferior cervical ganglion in Animal 5 was explained by histological confirmation from sections of the vagosympathetic trunk of the area stimulated. Chains of nerve cells were found among the bundles of fibers for a short distance along the course of the trunk. Apparently the numbers of cell bodies of neurones of this type are not aggregated in sufficient mass for gross evidence of a ganglion. Nevertheless, their presence in sufficient quantity to serve as a microganglion on the efferent dilator pathway is established.

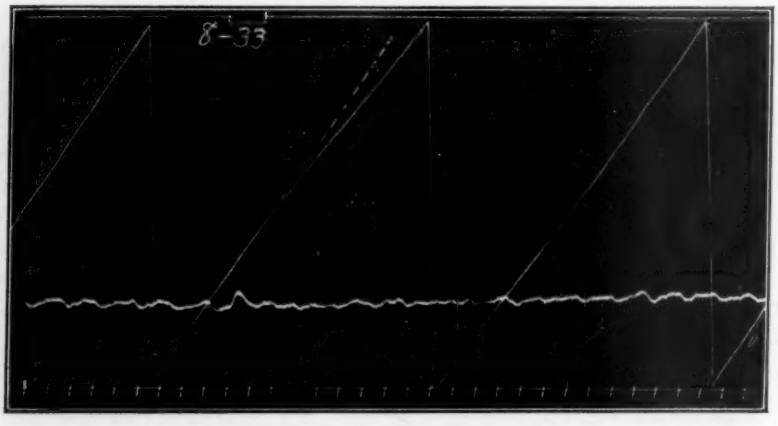

Fig. 3.—Dog. 8. Test 33: This record illustrates coronary constriction upon stimulating the superior cardiac nerve in the normal animal after atropine. (Reduced to 60 per cent.)

PROTOCOL III

Dog. 8.—Wt. 5.1 kg. Heparin, atropine. Had previously been injected with ephedrine and adrenalin.

Test 33: Stimulation of the right superior cardiac nerve of the normal animal, 6 cm.

TIME	BLOOD PRESSURE	PER CENT CHANGE	HEART RATE	PER CENT CHANGE	CORONARY FLOW	PER CENT CHANGE
10″ before	37.0		207		90.0	
15″ after	36.0	–3	213	3	78.0	–13
30″ after	37.5	1	213	3	76.0	–16
60″ after	39.0	5	213	3	82.0	– 9
120″ after	41.0	11	213	3	91.6	2
165″ after	41.0	11	213	3	96.0	7

CORONARY RESPONSE OF THE SUPERIOR AND INFERIOR CARDIAC NERVES BEFORE AND AFTER DEGENERATION OF THE VAGUS

The cardiac nerves at and below the inferior cervical ganglion of the dog are mixed trunks. The gross anatomy of the relations of the inferior cervical ganglion and vagosympathetic trunk and the origin of the cardiac branches which these contribute to the cardiac plexus were described in the dog by Schmiedeberg[5] in 1871, Pavlov[6] in 1887, and

Keng[7] in 1893. Schmiedeberg demonstrated the presence of cardiac inhibitor and accelerator neurones in these nerves, but coronary neurones were then unknown.

The superior cardiac nerve from the inferior cervical ganglion, the *nervus cardiacus superior* of Schmiedeberg, is the main trunk from the vagosympathetic complex to the cardiac plexus. It arises either directly out of the inferior cervical ganglion or from the ganglion and trunk in common with the recurrent laryngeal, from which it quickly separates as an independent nerve. It contains coronary neurones inseparably mixed with the cardiac neurones in varying proportions.

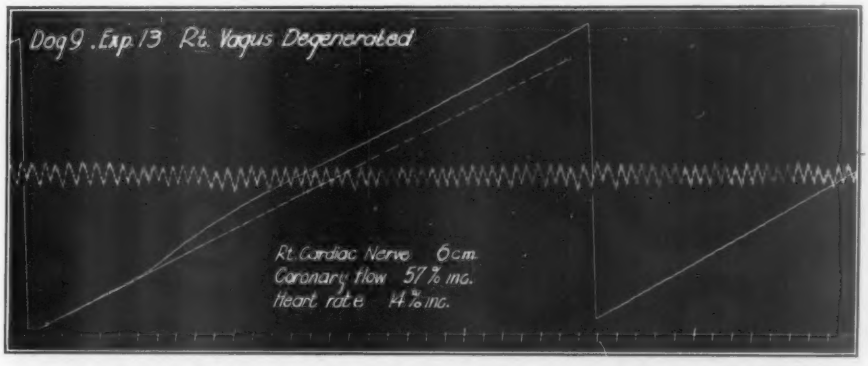

Fig. 4.—Dog 9. Test 13: Reaction of the coronary flow to stimulation of the right superior cardiac nerve, 127 days after vagosection above the ganglion nodosum. The coronary dilation shows a prompt increase of 57 per cent, lasting for only a few seconds, as contrasted with the dilation shown in Fig. 2, Test 7. (Reduced to 54 per cent.)

PROTOCOL IV

Dog 9.—Wt. 10.7 kg. Heparin 60 mg. per kilogram. Blood pressure equalized. Donor blood used.

Test 13: Stimulation of the superior cardiac nerve, a branch of the recurrent laryngeal about 1 cm. from the inferior cervical ganglion.

TIME	BLOOD PRESSURE	PER CENT CHANGE	HEART RATE	PER CENT CHANGE	CORONARY FLOW	PER CENT CHANGE
15″ before	85.0		162		31.1	
12″ after	85.0	0	180	11	48.9	57
30″ after	83.5	−2	156	−4	38.5	24
45″ after	83.0	−2	156	−4	31.3	1
75″ after	84.0	−1	156	−4	31.2	0
105″ after	84.5	−1	156	−4	34.0	9
150″ after	84.0	−1	156	−4	34.0	9
210″ after	85.5	1	156	−4	34.2	10

Stimulation of the *nervus cardiacus superior* in dogs having a normal vagus but treated with atropine usually produces coronary constriction. But at times coronary dilation predominates. Figure 3 presents the coronary constrictor type of reaction under these conditions. The decrease in flow from the coronary sinus amounted to 16 per cent in the test figured.

Stimulation of the superior cardiac nerve after the vagus nerve has degenerated never produces coronary constriction, but does induce a pronounced coronary dilation of 50 to 60 per cent and more. In Animal 9, Test 13, Fig. 4, the dilation amounted to a 57 per cent increase in the flow from the coronary sinus. One rarely secures such extreme coronary dilation in response to stimulation of the normal mixed cardiac nerve because of the neutralizing effects of antagonistic neurones. The volume of dilation obtained in the absence of coronary constrictor neurones is, therefore, the best graphic measure of the total available reflex dilation in the normal animal.

Stimulation of the superior cardiac nerve in the normal animal before atropine also produces very pronounced cardiac inhibition. In the atropinized animal inhibition is lost, and coronary constriction and

Fig. 5.—Dog 5. Test 46: Increase of the coronary flow upon stimulating the inferior cardiac nerve arising out of the spray of filaments below the right inferior cervical ganglion, 4 cm. The right vagus was cut 22 days earlier. (Reduced to 50 per cent.)

cardiac acceleration are present. After vagus degeneration, coronary dilation and cardiac acceleration remained as shown in Dog 9, Test 13, Fig. 4. These reactions offer a convenient and decisive analysis of the physiological content of the terminal cardiac pathways.

We have obtained responses similar to the above from stimulation of the total vagosympathetic trunk and from a group of small nerves just below the inferior cervical ganglion (Fig. 5, Dog 5, Test 46).

The superior cardiac nerve of the dog is indeed the chief efferent pathway for the constrictor control of the coronary arteries. Although some constrictor fibers are present in the *nervus cardiacus inferior* most of the coronary constrictor neurones run in quite direct course from their origin in the medulla down the vagosympathetic sheath, through the inferior cervical ganglion into the superior cardiac nerve and reach

PROTOCOL V

Dog 5.—Wt. 13.5 kg. Blood pressure equalized. Right vagus sectioned above the ganglion nodosum, twenty-two days before testing. The superior sympathetic ganglion not isolated from its peripheral branches.

Test 46: The main division to the cardiac plexus from the spray of nerves arising just below the inferior cervical sympathetic ganglion was stimulated 4 cm.

TIME	BLOOD PRESSURE	PER CENT CHANGE	HEART RATE	PER CENT CHANGE	CORONARY FLOW	PER CENT CHANGE
10″ before	65.5		174		88.4	
20″ after	68.0	4	324	86	141.6	60
50″ after	64.0	–2	249	43	103.4	17
75″ after	65.0	–1	204	17	96.8	10
120″ after	65.5	0	180	3	90.0	2
160″ after	62.0	–5	174	0	95.4	7

their distribution in the coronary blood vessels via the cardiac plexus. After degeneration of the vagus there is left unopposed the entire pattern of the coronary dilator system.

In the absence of the great mass of coronary constrictor neurones, it has been easier to follow the course of the dilators from their origin in the thoracic spinal cord, through the sympathetic system in the great fanlike spread from the superior cervical sympathetic to the sixth thoracic spinal ganglion, and via the branches of these ganglia also through the constituents of the cardiac plexus to the coronary vessels. A very interesting part of this body of information is the doubling back within the vagosympathetic paths of the postganglionic neurones of the middle and superior cervical ganglia. One may assume that in man the postganglionic neurones run in the superior and middle cardiac nerves, which in the human arise from the superior and middle cervical ganglia.

The presence of nerve cells along the course of the lower cervical sympathetic trunk of the dog that are clearly homologous with the middle cervical ganglion seems not to have been recorded hitherto in the literature.

SUMMARY

1. Vagosection was performed above the ganglion nodosum. The animals were allowed to recover and the nerves to undergo a variable period of degeneration and repair after which functional tests were applied.

2. Dogs with vagosection exhibit a total, or almost total, loss of coronary constriction in response to cervical vagosympathetic stimulation. Two animals have shown a mild degree of coronary constriction after cervical dilator control was reduced by injections of nicotine into the cervical sympathetic ganglia.

3. These more distally placed coronary constrictor neurones have only a moderate total effect and are not always present. A satisfactory

explanation of this occasional type of animal is that some few neuroblasts have migrated distally in early embryonic development.

4. The loss of coronary constriction after vagotomy and degeneration indicates that the vagus is the sole pathway of the efferent coronary constrictor nerves.

5. After the coronary constrictors are degenerated, stimulation of the cervical vagosympathetic produces coronary dilation of variable amount.

6. Coronary dilation from stimulation of the cervical vagosympathetic trunk after vagal degeneration does not occur in all animals, and varies in amount from nothing to a medium degree of dilation among those animals in which it is present.

7. There is greater reaction to stimulation of the lower cervical region just above the inferior cervical ganglion. A definite palpable middle cervical ganglion is rarely present in the dog. Histological sections, however, show that strands of nerve cells may be present among the bundles of axones of the vagosympathetic trunk at approximately the region of the middle cervical ganglion. These cells function as links in the chain of efferent coronary dilator pathways.

8. Cardiac inhibitory fibers were completely absent from the degenerated vagi of the animals reported in this series.

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THE TEMPERATURE OF THE FLARE AS AN INDEX OF THE INTENSITY OF THE HISTAMINE SKIN REACTION*

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THE histamine skin reaction is used widely as a test of circulatory efficiency in the study of peripheral circulatory disturbances. In 1927, Thomas Lewis[1] demonstrated that it consists of three distinct responses: (1) a local dilatation of the capillaries which causes a purplish areola about the site of introduction into the skin, (2) an increased capillary permeability which results in a wheal at the site of injection, and (3) a dilatation of the surrounding arterioles which is visible as a red flare. Since that time it has been firmly established as a valuable test of local circulatory efficiency.[2] The technic of the test has been modified since it was first described by Lewis. As now performed by us,[3] it consists of an intradermal injection of a 1:2,000 solution of histamine in 0.5 per cent novocaine in an amount sufficient to produce a wheal 2 mm. in diameter. Normally a purplish border 1 mm. in width appears within from 20 to 30 seconds around this primary wheal. In from 1 to 2 minutes there is an irregular increase in the size of the primary wheal to form a secondary wheal. A flare about 3 cm. in diameter makes its appearance in about 2 minutes and gradually increases in intensity, reaching its height in 10 minutes. The use of the novocaine with the histamine makes the test painless without altering the intensity of the reaction.

The usual criterion of the intensity of the histamine reaction is the rapidity of the development and the intensity of the flare. We have noticed that in normal individuals there are marked variations in the size and visible intensity of the flare which depend to a certain extent upon whether the skin is light or dark, and hairy or nonhairy. In negroes, for example, it is almost impossible to read the flare reaction. This test, furthermore, suffers as a standard of circulatory efficiency since the grading of the intensity of the flare is a matter of opinion, and the reading varies with each examiner.

These difficulties led us to search for a more objective means of determining the intensity of the histamine flare and thus of estimating the efficiency of the skin circulation. The determination of the temperature change in the area of the flare appeared to us to be a more accurate and objective measure of the histamine skin reaction. Since the temperature of the skin is dependent upon the circulation within the skin when all

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other factors such as room temperature, etc., are kept constant, the measurement of the temperature of the flare should eliminate such variables as the color and hairy distribution of the skin and the visual acuity of the examiner and should thus standardize the grading of the histamine skin reaction.

METHOD

Studies were made in both upper and lower extremities in twelve normal individuals of various complexions and in eight individuals with peripheral circulatory disturbances. These tests were made in a room at constant temperature (20 to 22° C.). The individuals were examined while resting horizontally. The areas to be examined were marked, and their temperatures were taken with a mercury skin thermometer every five minutes until several readings were constant. Sufficient solution (1:2,000 histamine in 0.5 per cent novocaine) was then injected intradermally in the marked areas to make a wheal 2 mm. in diameter. The temperature of the flare that resulted was measured every five minutes, and its visible intensity was noted until it began to disappear.

OBSERVATIONS

The averaged results obtained in twelve normal individuals are shown in Table I. In each case, as in the typical normal record shown in Table II, the temperature curve of the flare rose very rapidly in the

TABLE I

AVERAGED MAXIMUM TEMPERATURE OF HISTAMINE FLARES IN NORMAL INDIVIDUALS*

		3 BLOND FEMALES	3 BLOND MALES	3 BRUNET MALES	3 NEGRO MALES
Above elbow	Visible intensity	4	4	4	2
	Temperature	34.8	34.6	33.6	33.8
Below elbow	Visible intensity	4	4	4	2
	Temperature	34.0	34.2	33.4	33.8
Above wrist	Visible intensity	4	4	4	2
	Temperature	33.8	33.8	33.2	33.6
Dorsum of hand	Visible intensity	4	4	4	2
	Temperature	34.2	34.0	34.2	34.0
Dorsum 3rd finger	Visible intensity	4	4	4	2
	Temperature	34.0	33.6	33.6	33.6
Above knee	Visible intensity	4	4	4	2
	Temperature	34.0	33.8	33.6	33.4
Below knee	Visible intensity	4	4	4	2
	Temperature	33.8	33.8	33.0	33.2
Above ankle	Visible intensity	4	4	4	2
	Temperature	33.0	33.2	33.4	33.4
Dorsum of foot	Visible intensity	4	4	4	2
	Temperature	33.0	33.0	32.4	32.6

*Temperature in centigrade scale; visible intensity 1 = grade plus 1, 2 = grade plus 2, etc.

first 5 minutes, then slowly until it reached its height in 15 to 20 minutes after the injection. It was sustained at this level for 5 to 20 minutes and then dropped slowly to normal in from 60 to 120 minutes. The

visible flare reaction was similar, although in the brunets and negroes it was not so marked as in individuals of lighter complexion. The temperature of the flare, however, rose in these individuals, as it did in the other normals in whom there was a marked visible flare. In several instances in the negroes there was a rise in the temperature of the skin around the site of injection of the histamine even in the absence of a visible flare.

TABLE II

COMPARISON OF THE VISIBLE INTENSITY AND THE TEMPERATURE OF THE HISTAMINE FLARES IN A NORMAL BRUNET MALE

		0	5′	10′	15′	20′	25′	30′	45′
Above elbow	Visible intensity		4	4	4	4	4	4	3
	Temperature	30.6	32.6	33.2	33.8	33.8	33.0	33.2	31.8
Below elbow	Visible intensity		4	4	4	4	4	4	3
	Temperature	30.2	32.0	32.8	33.2	33.4	32.8	33.0	31.4
Above wrist	Visible intensity		4	4	4	4	4	4	3
	Temperature	29.2	32.2	32.8	33.2	33.4	33.0	33.0	31.4
Dorsum of hand	Visible intensity		3	3	4	4	4	4	3
	Temperature	29.6	32.0	33.0	33.8	34.0	33.8	33.2	31.6
Dorsum 3rd finger	Visible intensity		3	3	4	4	3	3	3
	Temperature	29.0	32.0	32.8	33.8	34.0	33.6	33.0	31.4
Above knee	Visible intensity		3	4	4	4	4	4	3
	Temperature	30.8	33.0	33.0	33.8	33.6	33.4	33.0	32.0
Below knee	Visible intensity		3	3	4	3	3	3	3
	Temperature	30.0	32.0	32.6	33.0	33.0	32.4	32.4	31.0
Above ankle	Visible intensity		2	3	3	3	3	3	2
	Temperature	29.0	32.4	33.0	33.2	33.4	33.4	33.2	30.0
Dorsum of foot	Visible intensity		3	3	3	3	3	3	2
	Temperature	27.8	31.0	31.8	32.4	32.4	32.4	32.0	28.2

The temperature of the flares at the height of the reaction varied from 32.8-34.6° C. (33.6° C. av.), on the dorsum of the hand and fingers, to 33.8-35.0° C. (34.6° C. av.), above the elbow. In the lower extremities the temperature varied from 31.2-33.0° C. (32.0° C. av.), on the dorsum of the foot, to 33.0-34.2° C. (33.6° C. av.), above the knee. The temperatures in blond females and males averaged from 0.5 to 1.0° C. higher than those of brunets and negroes.

TABLE III

COMPARISON OF HISTAMINE FLARES IN NONHAIRY AND HAIRY SKIN OF FOREARM IN A NORMAL BRUNET MALE

		0	5′	10′	15′	20′	25′	30′
				Volar Surface (Nonhairy)				
Above elbow	Visible intensity		3	4	4	4	4	4
	Temperature	30.4	32.2	33.0	33.8	33.8	34.0	34.0
Below elbow	Visible intensity		3	4	4	4	4	4
	Temperature	29.8	32.0	33.0	33.2	33.6	33.6	33.2
Above wrist	Visible intensity		4	4	4	4	4	4
	Temperature	29.2	32.2	32.8	32.8	33.2	33.2	32.6
				Dorsal Surface (Hairy)				
Above elbow	Visible intensity		3	3	4	4	4	3
	Temperature	30.2	32.4	33.2	33.2	33.4	33.0	33.0
Below elbow	Visible intensity		3	3	4	4	4	3
	Temperature	30.0	32.2	32.8	32.8	33.4	32.8	32.8
Above wrist	Visible intensity		3	3	4	4	4	3
	Temperature	29.2	32.0	32.6	33.0	33.0	33.2	33.2

Table III is a comparison of the visible intensities and the temperatures of histamine flares in similar areas of hairy and nonhairy skin in the same individual. There was a definite lag in the development of the visible intensity of the flare in the hairy as compared to the nonhairy skin, but the temperature of the flares in the similar areas of skin rose to the same levels simultaneously.

To determine the reliability of our visible readings of the flare intensity as an accurate objective standard and index of the amount of blood in the skin, a list was made of the highest and lowest temperatures obtained in flares whose visible grade was from 1-plus to 6-plus. This is shown in Table IV. We found that the temperatures of the

TABLE IV

LOWEST AND HIGHEST TEMPERATURES OBTAINED IN FLARES OF VARIOUS GRADES OF VISIBLE INTENSITY

VISIBLE GRADE	TEMPERATURE (C.)	
	LOWEST	HIGHEST
Plus 1	27.2°	30.0°
2	27.6°	33.6°
3	29.4°	33.0°
4	32.0°	35.4°
5	34.4°	35.2°
6	33.0°	36.0°

various grades of visible intensities were not constant and that the difference between the lowest and highest temperatures of flares of a given visible intensity grade was as high as 6° C. In many cases flares of the same temperature were given visible grades differing as much as 3-plus. These marked variations in the grades of the visible flare reactions even when judged by one experienced in these tests, together with the presence of differences in the visible intensities of flares in hairy and nonhairy skin and the difficulty in reading the visible intensity in dark-skinned individuals, when compared with the uniformity and constancy of the *temperatures* of the flares, indicate that the temperature of the flare is a more definite and reliable index of the skin reaction to histamine than is its visible intensity.

The visible intensity and the temperature of the flares were then compared in 8 cases of peripheral circulatory disturbances, namely, 3 cases of arteriosclerosis, 3 cases of thrombo-angiitis obliterans, and 2 cases of vasospastic disease of the extremities. The results in a typical case of each of these three conditions are shown in Tables V and VI. In each of the six cases of organic vascular occlusion, as in the typical cases shown, the temperatures of the flares were within the normal limits determined above (Table I) in the parts of the extremity that had a normal circulation and below the normal limits in those parts in which the circulation was deficient. The circulatory efficiency was de-

TABLE V

COMPARISON OF THE VISIBLE INTENSITY AND THE TEMPERATURE OF THE HISTAMINE FLARES IN CASES OF ORGANIC VASCULAR OCCLUSION

		B. S.—THROMBO-ANGIITIS OBLITERANS				J. G.—ARTERIO-SCLEROSIS	
		RIGHT EXTREMITY (DISEASED)		LEFT EXTREMITY (NORMAL)			
		0	15′	0	15′	0	15′
Above knee	Visible intensity		4		4		3
	Temperature	30.4	33.2	30.4	33.6	30.8	33.0
Below knee	Visible intensity		4		4		2
	Temperature	30.0	33.0	30.2	33.2	30.8	32.2
Above ankle	Visible intensity		3		4		2
	Temperature	28.6	30.4	29.2	33.2	30.0	31.2
Dorsum of foot	Visible intensity		2		3		0
	Temperature	26.0	27.6	28.2	32.8	25.0	25.8

TABLE VI

COMPARISON OF THE VISIBLE INTENSITY AND THE TEMPERATURE OF THE HISTAMINE FLARES IN A CASE OF VASOMOTOR DISTURBANCE OF THE EXTREMITIES

		P. N. VASOMOTOR DISTURBANCE						
		0	5′	10′	15′	20′	25′	30′
Above elbow	Visible intensity		6	6	6	6	5	5
	Temperature	32.6	35.2	36.0	36.0	35.4	35.2	35.0
Below elbow	Visible intensity		6	6	6	6	6	5
	Temperature	32.4	34.4	35.2	35.6	35.2	35.0	34.4
Above wrist	Visible intensity		6	6	6	6	6	6
	Temperature	31.8	34.4	35.2	35.2	35.2	35.0	34.6
Dorsum of hand	Visible intensity		6	6	6	6	6	6
	Temperature	31.0	33.8	34.6	35.2	34.6	34.0	33.4
Dorsum of 3rd finger	Visible intensity		6	6	6	6	6	4
	Temperature	26.6	33.8	34.4	35.2	34.0	33.0	32.8

termined by the subjective symptoms and the objective signs, which included arterial pulsations, the oscillometric index, the color and trophic changes in the skin, and the visible flare reactions. In the case of thrombo-angiitis obliterans (Table V) the circulation in the left lower extremity was determined to be normal. The right foot was red; trophic changes were present in the foot and in the lower one-third of the leg; the dorsalis pedis and posterior tibial pulsations were absent, and the oscillometric index in the foot was 0. In the diseased extremity the visible flare reaction on the dorsum of the foot was 2-plus, and the temperature of the flare rose only to 27.6° C. from a starting temperature of 26.0° C. In the upper part of the leg and in the thigh, where subjective and objective signs pointed to an efficient circulation, and in the normal left extremity the temperatures of the flares were within normal limits.

The patient with arteriosclerosis (Table V) had beginning gangrene of the toes. The temperature of the flare about the site of the histamine injection was only 25.8° C. on the dorsum of the foot, where the circulation was very poor; 31.2° C. above the ankle; and within the normal limits (33.0° C.) above the knee where the circulation was good.

The comparisons made in these six cases suggest that temperatures of flares which are below the established normals are indicative of deficient circulation.

In one case of vasomotor disturbance of the upper extremity (Table VI) the visible flare reactions and the temperature rise in the flare areas were greater than in our normal series. Although the starting temperature on the dorsum of the third finger was only 26.6° C., the visible flare reaction at 15 minutes was 6-plus, and the temperature of the flare was 35.2° C. This marked reaction to histamine has been present in a few of the patients with vasomotor disturbance whom we have examined and will require further study for an explanation. In the other case of vasomotor disturbance of the extremities studied in this series, the temperatures of the flares were within normal limits.

SUMMARY

1. A. The temperature of the histamine flare reaches its height in 15 to 20 minutes.

B. The average temperature of the flares in the normal upper extremity varies from 33.6° C. on the dorsum of the third finger to 34.6° C. above the elbow, and in the normal lower extremity from 32.0° C. on the dorsum of the foot to 33.6° C. above the knee.

C. The temperature of the flare is from 0.5° C. to 1.0° C. higher in individuals with light complexions than in brunets and negroes.

D. In contrast to the visible intensity there are no appreciable differences between the temperatures of the flares in hairy and nonhairy areas.

2. The temperature of the flare is a more accurate index of the histamine skin reaction than is the visible intensity of the flare.

3. Failure of the temperature of the flare to rise to the above mentioned levels is suggestive of circulatory deficiency.

I wish to thank Dr. L. N. Katz for his advice in preparing this report.

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ALTERNATION PHENOMENA IN THE ELECTROCARDIOGRAM

Occurrence in a Patient With Active Carotid Sinus Reflex*

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ALTERNATION in strength of pulsations in the peripheral vessels (pulsus alternans) is a not uncommon clinical finding, long recognized, and in most instances considered by observers to suggest a poor prognosis. It may be detected by some type of photographic or mechanical recording device—more simply by the use of blood pressure cuff and stethoscope or, if marked, by palpation. Only rarely has it been associated with corresponding changes in the electrocardiogram.

Alternation of the various waves in the electrocardiogram may occur, and is usually unaccompanied by corresponding changes in the pulsation of the peripheral arteries.

Our patient has been studied for a period of about three and one-half years because of the occasional occurrence of convulsions and syncope. His electrocardiograms seemed unique in that they demonstrated alternation in the heights of the T-waves with changes in the intraventricular conduction. This phenomenon was found not only after premature contractions but also in the absence of premature contractions. In the absence of premature contractions, the electrical alternation was not associated with large pulse waves in the arteriogram. The patient had an extremely active carotid sinus reflex which manifested itself very strongly on his cardiovascular mechanism. At no time has the production of this reflex induced the alternation.

CASE REPORT

A. P., a white, sixty-three-year-old Polish janitor, with an unusually good health record, was found unconscious on the floor of the factory, Nov. 20, 1931. He had been an employee of the Eastman Kodak Company for eleven years when this study was started. His record at the medical department from 1920 to 1931 revealed a series of blood pressure determinations with systolic pressures varying from 140 to 180, and diastolic from 80 to 90 mm. On one occasion, in 1928, a few premature contractions were heard.

There was no history of trauma and no signs suggesting it. At all interviews and examinations conducted at intervals up to the date of onset he had been free from complaints. There was no history of previous "spells," dyspnea, precordial pain, palpitation, vertigo, or edema. He had been a moderately heavy user of alcohol, coffee, and tobacco. The family history was negative, and he denied all past illnesses. Because of the first attack of syncope, he was not permitted to return to work for one month.

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An examination three weeks later showed a well-developed male, weighing 156 pounds, and measuring 5 ft. 7 in. in height. There was no dyspnea, cyanosis, or edema. Ocular movements were normal. The eye balls were rather prominent, but there was no exophthalmus or lid lag. The pupils were normal, and the optic discs were well outlined. Evidence of moderate retinal sclerosis was seen. Marked pyorrhea alveolaris was present. There was evidence of pulmonary emphysema. The heart was not enlarged to percussion. The rhythm was regular, and there were no murmurs or thrills. The rate was 112 per minute; blood pressure was 130/80. An occasional premature contraction was heard. The abdomen was negative. Pulsus alternans was not detected when the blood pressure was taken.

The neurological examination was negative except for the occasional appearance of a coarse tremor of the extremities, noticed when the patient was perturbed. This seemed definitely under voluntary control.

Roentgenogram Examination.—Heart film at a distance of six feet showed a transverse type of heart and a widening of the shadow of the great vessels. Internal diameter of chest was 28.5 cm.; total transverse diameter of heart, 13.25 cm.; midline to left border, 10.0 cm.; midline to right border, 3.25 cm.; great vessels, 7.0 cm.

Skull examination, including roentgenography, was negative for evidence of fracture or other abnormalities. Stereoscopic films of the chest in 1922 showed evidence of inactive tuberculosis at both apices, and follow-up films of the chest showed no change (Dr. E. K. Richard).

The patient was taken to the Rochester General Hospital where he remained for three days. While there, his temperature varied from 99° to 101° F., he became irrational, threatened to jump from a window, and finally had to be restrained. During an examination, he suddenly emitted a cry, became spastic, and assumed the position of opisthotonos. His blood pressure, before the convulsion, was 158/80 and his pulse was 84. Afterward his blood pressure was 178/80; his pulse was not recorded. This episode lasted for five minutes, and during this time there was no loss of sphincter control. However, a bilateral positive Babinski reflex was noted, and there was a loss of the normal corneal reflex. The right extremities were slightly more spastic than the left, and the patient became very cyanotic. A short time later the mental aberration disappeared.

Laboratory Findings.—The blood Wassermann and Kahn tests were negative. Erythrocytes numbered 4,650,000; leucocytes, 6,000; and hemoglobin (Dare) measured 90 per cent. The blood smear was normal. Examination of the urine showed an absence of albumin and sugar, a negative sediment, and a specific gravity of 1.022. The blood sugar (fasting) was 102 mg. per cent; and blood nonprotein nitrogen was 32 mg. The spinal fluid pressure was 8 mm. Hg; the Pandy test was negative; spinal fluid sugar was 95 mg. per cent; no leucocytes were recognized, and 25 erythrocytes were counted per cubic millimeter. Cultures were sterile.

Course.—The patient remained symptom free until eight months later. He was seen at frequent intervals. During this time his blood pressure varied from 130 to 160 systolic and 84 to 102 diastolic. At this time a second period of unconsciousness occurred while he was attending his usual duties at the factory. An examination made a few minutes after the incident showed stertorous respirations and clonic movements of his lower jaw. The pulse rate was 96 and regular. His heart sounds were distant, and no murmurs were heard. There was a slight contusion behind his left ear. The patient was unable to account for either the first or second period of unconsciousness. He denied any recent overindulgence in alcohol, although he admitted that he had been taking small amounts regularly. Shortly after this, another attack of syncope occurred while the patient was at home. The patient was somewhat indefinite in his account of this last "spell."

Because of the hazard incident to his employment, he was retired from the company in February, 1933, and is now receiving a pension. He is able to do light work about the premises of his home.

DISCUSSION

We originally became interested in this patient because of our attempts to explain the cause of his syncope and convulsions. Numerous electrocardiograms, taken during the course of our investigation, showed alternation of certain of the complexes.

A rather extensive review of published tracings illustrating the phenomenon of alternation would seem to indicate that the findings encountered in this patient are unique. We have not found an identical

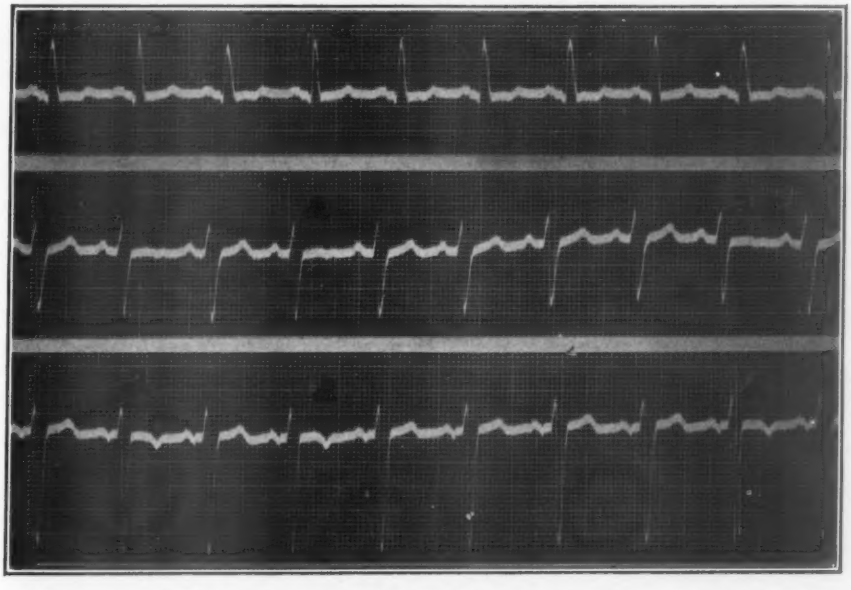

Fig. 1.—Leads I, II, and III, showing the rhythmic occurrence of electrical alternation. The unusual beats are marked *a*. The above periodicity repeated itself a number of times without interruption in all leads of the tracing taken on this date. Other tracings have shown alternation without the above periodicity. No premature contractions were encountered on this date.

record. The electrical alternation occurred in most of the thirty tracings taken during the three and one-half years of observation. Because of this apparent rarity, the case seemed deserving of a brief report.

The electrocardiograms of our patient showed predominant beats, characterized by a widening of the intraventricular conduction time (QRS measured 0.13 second to 0.14 second) (see Figs. 1, 2*A*, and 2*B*). There was slurring and notching of the QRS complexes in all leads. In addition to the above there were found unusual cycles characterized by a decrease in intraventricular conduction to 0.10-0.12 second with a change in the electrical axis of the T-waves. These unusual cycles were of two types and were classified according to the presence or absence

of changes in the arteriogram. We have designated these unusual cycles arbitrarily as *a* cycles or *b* cycles. The *a* cycles were not associated with a change in the arteriogram. The *b* cycles occurred after premature contraction and were associated with changes in the arteriogram.

A rhythmic occurrence of the unusual or *a* beats (see Fig. 1) was found on only one occasion. Premature contractions were not found in any of the three leads of this particular record (about 50 cycles in each lead were taken). When the cycles in each lead of this electrocardiogram were marked off into groups of seven, it was found that the second and fourth beats of each of these groups were *a* beats. In tracings taken at other times the *a* beats were less regular in occurrence. More frequently these beats occurred a few times in each lead, sometimes separated by one of the "usual" beats; at other times, an isolated *a* beat

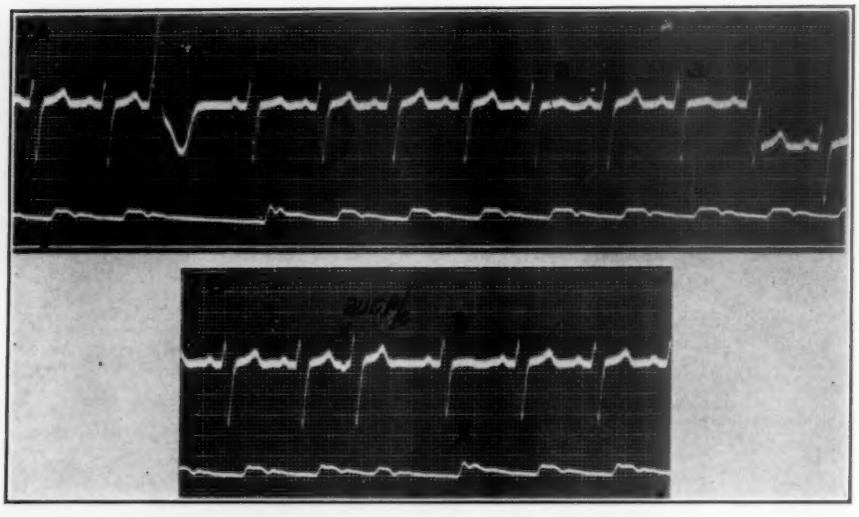

Fig. 2.—Lead II, showing electrocardiogram and brachial arteriogram. *A*, electrical alternation following ventricular premature contraction and associated large arterial waves; later electrical alternation without arterial wave changes. *B*, electrical alternation following auricular premature contraction and associated with arterial wave changes.

occurred. Never were two *a* beats found in succession. There was no change in the R-R or P-R intervals, irrespective of the type of cycle. The T-wave changes are not as clearly seen in the first lead as in the second and third leads.

The short QRS conduction time of the *b* cycles, occurring after premature contraction, suggests that an improvement in function may have resulted from the longer rest period (compensatory pause). This might be explained by a greater diastolic filling during the compensatory pause resulting in a larger stroke volume.

The prolongation of intraventricular conduction in the preponderant beats suggests so-called incomplete bundle-branch block. It would seem that a state of balance associated with transient improvement of con-

duction best explains the occurrence of the alternation waves (*a*). The absence of changes in the arteriograms accompanying these *a* beats and the occurrence with the *b* beats is difficult to understand—unless it is considered that the additional rest (compensatory pause) permits generation of greater mechanical force by the *b* beats (larger stroke volume). Our tracings are in many respects similar to ones obtained by Carter and Faulkner in their work on the suspended terrapin heart. In their experiments, the hearts were exposed to severe conditions never encountered in the living animal. They found alternating changes in intraventricular conduction and T-wave voltage. Dr. Harold E. B. Pardee was kind enough to review the electrocardiograms of this patient. He felt that the changes in QRS and T were due to functional variation in a portion of the heart muscles, resulting from what might be called a state of balance easily influenced by minor factors.

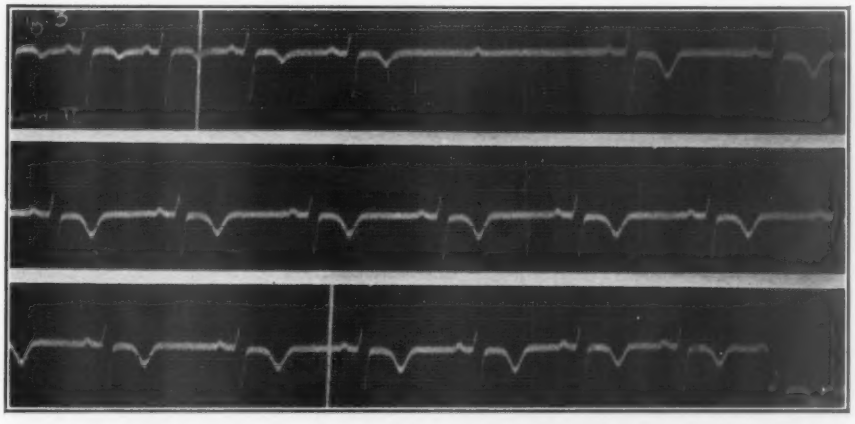

Fig. 3.—Lead II. Continuous strip of record showing the effect produced on the electrocardiogram by pressure on the left carotid sinus. Signals indicate application and removal of pressure. There is shown ventricular standstill for about 2.2 seconds, associated with a sudden drop in rate from 83 to 45 beats per minute, an increase of P-R from 0.16 to 0.20 second and T-wave changes. An abrupt drop of blood pressure occurred from 165/90 to 106/80.

We also took combined records showing the electrocardiogram and respiratory excursions and could demonstrate no relationship between the appearance of electrical alternation and the respiratory cycle. Nor did the administration of atropine or epinephrine affect the appearance of the electrical alternation. The absence of alternation in chest leads (front to back of chest) and the slight difference between the three types of complexes found in the conventional leads suggest that only a small area of the myocardium is involved. Pressure over either carotid sinus did not produce electrical alternation. Atropine abolished the carotid reflex; epinephrine did not.

In our attempt to ascertain the cause of his convulsions, we have considered ventricular standstill (Adams-Stokes syndrome), paroxysmal auricular or ventricular tachycardia, paroxysmal auricular or ventricu-

lar fibrillation, idiopathic epilepsy, brain tumor, and cerebral arteriosclerosis. Spontaneous hypoglycemia was ruled out by blood sugar studies. Idiopathic epilepsy usually occurs in the earlier decades. The lack of progression and absence of localizing signs since onset of symptoms three and one-half years before would seem to be evidence against a cerebral neoplasm. Escamilla[19] described the history of a patient who had convulsions quite similar to our patient's in whom he was able to demonstrate the etiology due to transient attacks of ventricular fibrillation. This, of course, is a very rare finding. Some other type of paroxysmal arrhythmia may be the cause of the syncope and convulsions in our patient, but we have not felt able to make a complete differential diagnosis.

We have also considered the possibility of explaining his syncope and convulsions on the basis of an increased activity of the carotid sinus reflex. It is of interest that the application of pressure over either carotid sinus produced the symptoms of blurring of vision, ear noises, vertigo, and marked facial pallor when the test was applied with the patient sitting. The symptoms were not noted when pressure was applied with the patient recumbent. It is possible that the application of carotid sinus pressure with the patient in the standing position might have produced more marked symptoms, but we were reluctant to assume the responsibility of possible injury to him. He was unable to induce the reflex by moving his neck briskly in various positions while standing.

Weiss and Baker[17] have attempted to explain the occurrence of convulsions, vertigo, and syncope on the basis of an overactive carotid sinus reflex. That this may be the explanation of our patient's symptoms is suggested, but not proved, by the electrocardiogram (see Fig. 3). In this tracing is seen a period of ventricular standstill lasting 2.2 seconds and an abrupt slowing of the rate from 83 to about 45 beats per minute. Simultaneous with these changes there occurred a drop of the blood pressure from 165/90 to 106/80.

REVIEW OF THE LITERATURE

Various types of electrical alternation have been described, one of the rarest being alternation of the P-wave alone as described by Chini,[4] Condorelli[8, 12] and also by Lewis.[2] T-wave alternation alone or with changes in the QRS complexes is more frequently encountered. Kapff[13] among others has described post-extrasystolic alternation in the height of the T-waves. The QRS complexes may be affected alone by this phenomenon and in this type of wave R is more often involved; variations in the S-wave are even more rare.[5] Alternation in height of the QRS complexes is occasionally found in hearts which have beaten rapidly (fatigue phenomenon of Winterburg).

Instances of modification of the entire QRS complex have been described in man by Condorelli[8, 12] in auricular fibrillation and by Galla-

vardin[6] and Smith[7] during ventricular tachycardia. Here the complexes at times regularly alternated in direction and shape. These last are probably not true examples of alternation but seem to represent premature contractions arising from different foci.

For an extremely comprehensive review of the literature on the subject, as well as a discussion of current theories concerning the phenomena, one should refer to the paper of Laubry and Poumailloux[9] and the recent monograph by Bruno Kisch.[18]

Experimental Work.—Condorelli found isolated alternation of R when he pinched the lower part of the sulcus terminalis of the rabbit and in another rabbit when he tied the collateral branch of the left descending coronary artery. Mines[3] appears to have been the first one to demonstrate electrical alternation without mechanical alternation. De Boer,[10] working on the frog heart, showed a number of simultaneous mechanical and electrical tracings in which the small T-waves corresponded with the large ventricular wave. Hering[11] found the large T-waves and large R-waves coincident. Condorelli[12] showed more often discordance between the heights of peaks R and T. De Meyer studied the electrocardiographic variations of the T-waves, which he considered an expression of small disturbances of systolic expulsion. Lewis,[2] in attempting to correlate experimental with clinical observations, felt that alternation in strength of the auricular contraction caused a corresponding variation in the ventricular contractions.

Otto[14] encountered variations of the T-wave when the aorta or the pulmonary artery was compressed suddenly, causing variations in the intracardiac pressure. Henrijean[15] experimentally demonstrated that the T-wave increased in proportion as the contraction diminished. In fact, when the heart was stopped, the greatest T-waves appeared while the electrocardiogram continued to be produced. If the contraction of the heart was brought about by massage, the T-waves decreased as the contraction increased.

Carter and Faulkner,[16] working on the suspended terrapin heart, demonstrated in the presence of mechanical alternation that there might be a great variability in the rate of spread of the excitation wave. They also showed that the speed of intraventricular conduction diminished as the muscle became exhausted. Distinct alternation of the intraventricular transmission interval was found in one of these experiments and seemed related to the degree of mechanical alternation.

SUMMARY

We have presented an unusual case demonstrating electrical alternation of the QRST complexes of the electrocardiogram without alternation of the pulse in a patient who had occasional attacks of syncope and convulsions. An active carotid sinus reflex was present and may have been a factor in producing his symptoms. Two types of unusual beats

were encountered. These were identical in the electrocardiogram, but those following auricular or ventricular premature contractions were associated with large waves in the arteriograms; those occurring in the absence of premature contractions were not associated with changes in the arteriogram. The patient has shown clinical improvement during a period of three and a half years of observation.

We wish to express thanks to Dr. W. A. Sawyer, medical director of the Eastman Kodak Company, for the opportunity for making these studies and also to Dr. J. M. Faulkner and Dr. H. E. B. Pardee for examining the electrocardiograms and for their helpful interest.

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Department of Clinical Reports

SYNCOPAL ATTACKS DUE TO A CONGENITAL ANOMALY OF THE RIGHT COMMON CAROTID ARTERY*

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OBSTRUCTION of the carotid artery may result from operative ligation, from aneurysm or arteriosclerosis, or from congenital anomaly —ligation and aneurysm being by far the most common causes of such obstruction. In spite of the efficient design of the arterial circle of Willis, cerebral anemia or infarction may result. The usual symptom produced is contralateral hemiplegia. Marked mental deterioration, syncopal attacks, epileptiform convulsions, and unilateral visual changes have been described. Neurological manifestations following ligation or aneurysm have been described by Todd[13] (1835), Hare and Holder[7] (1899), Shikare[12] (1921), Crawford[4] (1921), Courbon[3] (1926), Kampmeier and Neumann[10] (1930), Cohen and Davie[2] (1933), Dorrance[6] (1934), and others. Cases of arteriosclerotic obstruction of carotid vessels with resultant cerebral symptoms were reported by Broadbent[1] in 1875, Hunt[9] in 1914, and Moniz[11] in 1930. Congenital anomalies of the carotid artery of any significance are rarely reported in adults; two cases were reported in 1921, one by De Meyer,[5] and the other by Homans.[8]

The only case like ours, however, which we have found in the available literature is that reported by De Meyer. He described the case of a young man who, at the age of thirty-two years, began having syncopal attacks, ataxia, and profound asthenia; he became confused and his mental powers deteriorated. On physical examination the right common carotid artery was found to be greatly narrowed and the heart was in a median position.

REPORT OF CASE

The patient in our case was a country school teacher and farmer, fifty-two years of age, who came to the clinic complaining of dyspnea, fainting spells, and weakness. He stated that a physician had heard a heart murmur twenty-two years previously and that in the last five or six years the dyspnea on exertion had increased to a pronounced degree. Since about the age of thirty he had experienced frequent syncopal attacks. These attacks had always followed some unusually violent exertion, especially when such exertion was accompanied by excitement. The first attack he could recall had occurred after he had run to avoid a storm. He had reached the house and had sat down, when suddenly everything had turned black;

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his wife had helped him outdoors to get air. On another occasion he had been burning leaves and the fire had nearly got out of control; while violently attempting to pound it out with a stick, he had suddenly found himself lying face down on the ground with his mouth partly full of dirt. At another time an old friend had come to visit him, and as he had rushed quickly to greet him things had turned black, and he had fallen to the floor.

Although as a young man he had prided himself on his endurance and athletic ability, especially in running, he had later become known locally as a man who had "fits" when he exercised. As he grew older, these attacks had been induced more easily, but he had never had an attack except in connection with some unusual exertion. He had usually been able to tell when an attack was coming on; he would experience a strangling sensation in his throat, fight for breath, and perhaps call for help, and he would then become pale or cyanotic and fall in a brief faint. He would regain consciousness in a few seconds or few minutes. Witnesses had never observed muscular spasm; he had not been incontinent of urine and had never bitten his tongue.

While the patient was under observation in the hospital an attack came on after he had walked rapidly up and down the corridor. He suddenly turned white, sat down, and began to yell at the top of his voice. This continued for about two minutes. It was difficult to examine him at the time because of the commotion he created. His pupils were somewhat dilated; his extremities and face were quite cold; and perspiration was rather marked.

On physical examination the patient was found to be obese, and he looked considerably older than the stated age of fifty-two years. His blood pressure was 134 systolic and 78 diastolic; the pulse was totally irregular (auricular fibrillation), the rate being 80 beats per minute. Pulsation in the right common carotid artery was very feeble, whereas that in the left common carotid artery was normal. The radial pulses were equal. Expansion of the thorax was somewhat limited. The heart was markedly enlarged to percussion, the left border extending to the mid-axillary line. A systolic murmur could be heard over the whole precordium, but was loudest at the apex. The second pulmonic sound was somewhat accentuated. There were a few moist râles at the bases of both lungs. Otherwise, physical examination gave essentially negative results.

Vision in the right eye was 6/7, with correction, and in the left eye 6/12, with correction. The pupils were large; the reflexes were slow; and the fields were roughly normal. Fundoscopic examination revealed very little retinal arteriosclerosis. At rest, there was a slight arterial pulsation visible in the left retinal arteries. No pulsations were seen in the right eye. After exercise arterial pulsation became very marked in the left eye, but none was noted in the right eye. When the patient lay down, pulsations in the left eye were no longer visible. Changes in posture caused only slight changes in blood pressure. Urinalysis and examination of the blood, including the Kahn and Kline tests, gave negative results. Roentgenograms of the thorax disclosed nothing of significance, except the rather marked cardiac enlargement. The electrocardiogram showed a rate of 68 beats per minute, and auricular fibrillation with ventricular premature contractions, slurring of the QRS complex in Lead I, notched QRS in Leads II and III (QRS 0.10, 0.12, 0.12 seconds), and inverted T-waves in Leads II and III.

While under our observation the patient on several occasions became disoriented; his memory was very defective; he was quite garrulous; and he gave evidence of a serious degree of mental deterioration. Neurological examination gave no evidence of lesions in the central nervous system, and our opinion was substantiated that the cerebral anemia resulting from carotid inadequacy could best explain both the

mental symptoms and the attacks of syncope. A congenital defect of the right common carotid artery, perhaps associated with insufficient collateral connections through the circle of Willis, seemed to be the best explanation for these observations.

This case is of unusual interest for several reasons, one of which is our inability to find more than one other like it in the available literature. We believe that this patient undoubtedly has a congenitally underdeveloped right common carotid artery, and consequently an inadequate supply of blood to his brain. The probabilities are that he may also have some congenital defect of the communicating branches between the right and left sides at the base of the brain. We believe that his symptoms of cardiac insufficiency are attributable to two factors: (1) an old mitral endocarditis with probable stenosis, although the physical findings are not typical for this, and (2) obesity. We have no other adequate explanation to offer for the symptoms of cardiac insufficiency.

It is interesting to speculate upon why the patient's attacks began at the age of thirty years and not before. There is, we believe, at least a partial explanation for this. His weight had increased considerably, within a relatively short period, from 164 to 185 pounds (74 to 84 kg.). Because of the old mitral endocarditis, his cardiac reserve was probably not as great as it had been when he was younger, so that, with the inadequate common carotid artery on the right side, he was not able to maintain an adequate supply of blood to his brain during strenuous exercise. Other evidence that would seem to support this is that, as he became older and as the cardiac reserve continued to decrease, the attacks were more easily precipitated. We believe the mechanics responsible for this patient's symptoms are practically the same as those that are present in aortic stenosis. He did not have a hypersensitive carotid sinus.

The features to which De Meyer called attention in his case were the disorientation and confusion. These same features were present in our case and had become pronounced during the few months before we saw the patient. This was probably the result of the inadequate supply of blood to the brain, together with some sclerosis of the arteries of the central nervous system. We believe that if patients have attacks of unconsciousness, or syncope, and no adequate cause can be found, some congenital defect of the large vessels of the neck should be sought for as the cause.

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COMPLETE HEART-BLOCK IN HYPERTHYROIDISM*

Report of a Case

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ALTHOUGH disturbances in cardiac mechanism are frequently associated with hyperthyroidism, heart-block is rarely seen in this condition. Davis and Smith[1] have recorded six cases of heart-block in hyperthyroidism, but all of these followed acute infections. In a careful review of the literature they were able to find four similar instances. In the case reported here, however, it is believed that the heart-block has resulted from hyperthyroidism itself rather than from infection.

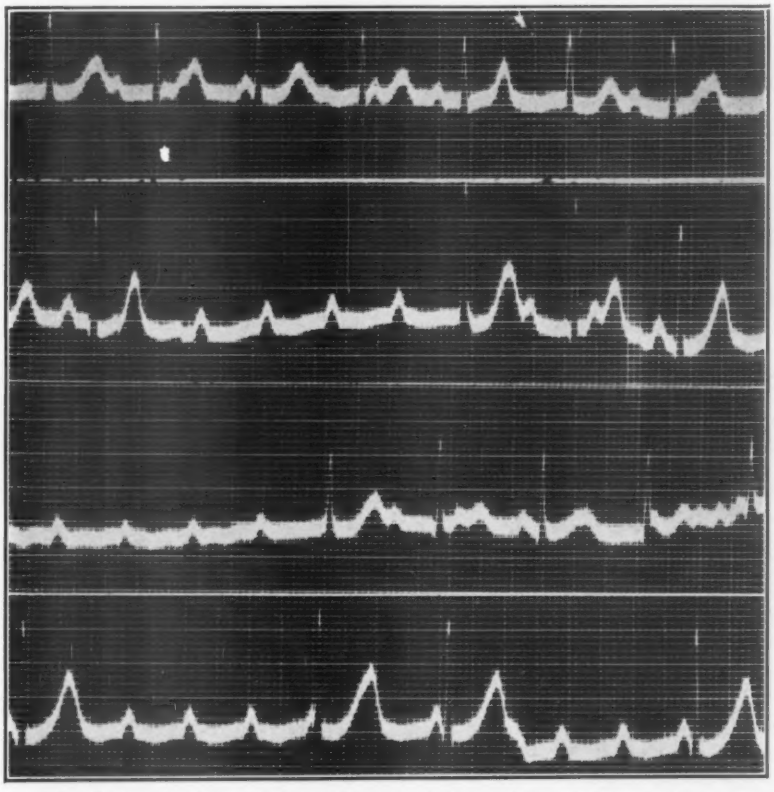

Fig. 1.—Usual four leads. Electrocardiogram taken July 4, 1935, showing complete heart-block.

CASE REPORT

A white housewife, thirty-nine years old, was admitted to the University Hospitals, July 4, 1935. While on a picnic she suddenly fainted. After a few moments she regained consciousness only to faint again shortly thereafter. This process

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recurred about fifty times during the day. On further questioning it was learned that she had had attacks of palpitation for about one year and had been "nervous" and subject to fatigue during this time. She had lost about twenty pounds, some of which, however, she regained. The history otherwise was of no significance.

On examination she was found to be a well-developed, well-nourished woman. The skin was moist. The thyroid gland was enlarged and adenomatous. The apex rate ranged from 60 to 70 beats per minute with rather long pauses of asystole at intervals. Isolated auricular beats could be heard, and auricular venous waves in the neck could be seen which were not associated with ventricular beats. Blood pressure was 130/80. Palpation over the precordium revealed no abnormalities. The heart borders were within normal limits. No murmurs were heard; lungs normal; no râles at bases; abdomen normal; no enlargement of liver or spleen; no edema. Admission temperature 38° C.

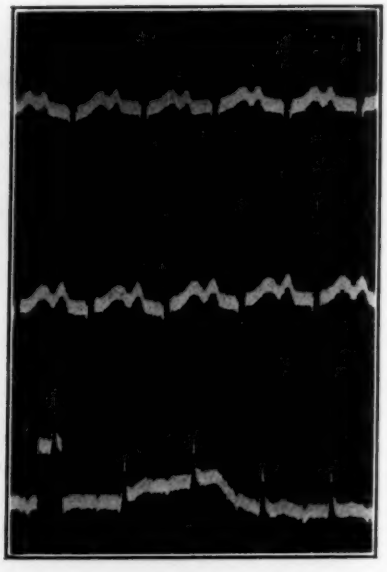

Fig. 2.

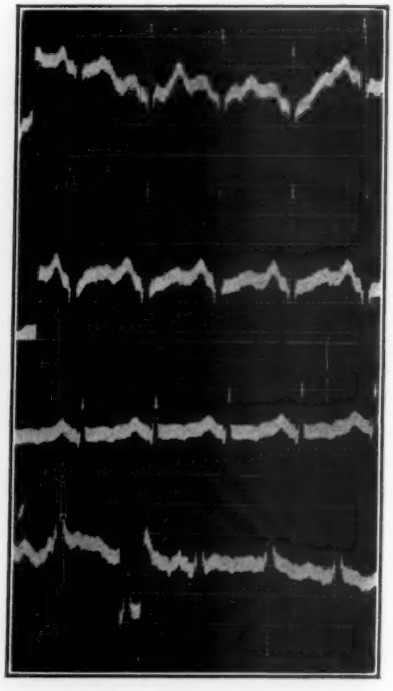

Fig. 3.

Fig. 2.—Usual three leads. Electrocardiogram taken July 10, 1935, showing sinus tachycardia with P-R interval of 0.24 sec. Lugol's solution administered since record shown in Fig. 1 was made.

Fig. 3.—Usual four leads. Electrocardiogram taken July 24, 1935, nine days after thyroidectomy. Shows normal mechanism.

A diagnosis of complete heart-block associated with hyperthyroidism was made. Electrocardiogram (Fig. 1) confirmed the diagnosis of heart-block. The basal metabolic rate on July 5, 1935, was +36 per cent. The white blood count was 8,200, with a normal differential count. Blood Wassermann test was normal. Blood urea nitrogen was 14 mg. and the plasma cholesterol, 106.

COURSE

Soon after admission atropine (1/30 gr.) was given hypodermically and produced no noticeable effect clinically or in the electrocardiogram. This was repeated later with the same result.

Lugol's solution, 5 minims t.i.d., was started July 6. This was increased gradually to reach 20 minims t.i.d. on July 14.

An electrocardiogram taken July 8 after approximately forty-eight hours of iodine therapy showed prolonged A-V conduction with dropped beats.

An electrocardiogram taken July 10 showed sinus tachycardia with P-R interval of 0.24 sec. (Fig. 2).

An electrocardiogram taken July 15 showed normal mechanism. The basal metabolism decreased to +3 per cent on this day, and operation was performed by Dr. C. H. Lenhart the same day. A large adenomatous thyroid was removed.

Lugol's solution was continued postoperatively. The progress was uneventful until July 18, when auricular fibrillation with a ventricular rate of 160 commenced. Digitalis was withheld as long as thought advisable, but finally 1½ grains were given because of the gravity of her condition. A similar dose was repeated in six hours after which the fibrillation ceased. A normal mechanism has continued since that time. (Fig. 3 shows electrocardiogram taken July 24.) She was last seen March 1, 1936, and was in excellent health.

DISCUSSION

Although the admission temperature of 38° C. was maintained for forty-eight hours, we do not believe that infection played any part in the production of the block. There was no leucocytosis and no evidence of infection on examination. The prompt response to Lugol's solution indicates that the block was a part of the thyroid toxicosis.

SUMMARY

A case of hyperthyroidism associated with heart-block is reported. The block disappeared under iodine therapy and did not recur after removal of the adenomatous thyroid.

The author acknowledges appreciation to Dr. R. W. Scott for his assistance in this case.

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A CASE OF ACQUIRED INTERVENTRICULAR SEPTAL DEFECT ASSOCIATED WITH LONG-STANDING CONGESTIVE HEART FAILURE*

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INTERVENTRICULAR septal defect is commonly a congenital lesion. The unusual cases of acquired septal disease are of necessity the result of a destructive process and may be divided into two types: (a) those due to bacterial endocarditis or a pyemic metastatic abscess and (b) those following an acute coronary vessel closure. Though rupture of the heart following an acute coronary closure is quite common, the septum usually escapes rupture on account of the extensive collateral circulation.

Reports of cases of rupture of the septum, associated with acute or chronic coronary vessel closure, have appeared in the literature from time to time. Additional instances have recently been added by Freeman and Griffin,[1] Kepler, Berkman, and Barnes,[2] and Sager.[3]

The following case is of interest in that the patient was known to have had coronary artery disease for some time, associated with an acquired healed septal defect which, from the type of lesion and healing, must necessarily have been of long duration. Despite this large defect he survived long enough to develop chronic congestive failure, which for a considerable period responded to the usual diuretic measures.

REPORT OF CASE

H. R., No. 19294, aged fifty-seven years, was admitted to the Montefiore Hospital on July 25, 1930, with a history of weakness, shortness of breath, and swelling of the legs and abdomen. He was known to have had hypertension for three years. On Sept. 2, 1929, after a restless night, he suddenly became unconscious, was cyanotic, had stertorous breathing, and blood trickled from his mouth. Unconsciousness lasted one and one-half hours and was followed by marked weakness, with which he was confined to bed. One month later he had a similar attack; altogether he had five such episodes, the last one occurring in December, 1930. Following his last seizure he had dyspnea on slight exertion, a diminished urinary output, and swelling of the legs and abdomen. Salyrgan had to be administered, and one week prior to admission to the hospital it was necessary to perform a paracentesis of the abdomen. He had received morphine for several months and had become addicted to its use.

Examination showed a fairly well-nourished, well-preserved, middle-aged man lying comfortably in bed. His lips were slightly cyanotic. The pupils were equal and constricted (morphine); the fundi showed marked sclerosis of the retinal vessels, with narrow irregular constricted arteries and arteriovenous constrictions. There was considerable dilatation of the veins of the neck in the upright position. The

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pulsations of the carotid arteries were visible bilaterally. The chest was of the emphysematous type, and there was bilateral effusion in the pleural cavities. The apical impulse was palpated at the fifth intercostal space just below the nipple line. A fine systolic thrill was palpable over this region, and a questionable presystolic apical murmur was heard. There was a prolonged systolic murmur audible over the entire precordium and base of the heart. It was louder at the apical region and in the ensiform area. The apical second sound was sharp and almost clicking, the pulmonic second sound greatly accentuated. The heart rhythm was regular. The blood pressure was 184/128. The radial arteries were moderately sclerotic, the pulses full and bounding.

X-ray examination of the chest showed bilateral hydrothorax, marked enlargement of the heart, the left border reaching almost to the left lateral wall. The electrocardiogram showed slurring of complexes and right axis deviation.

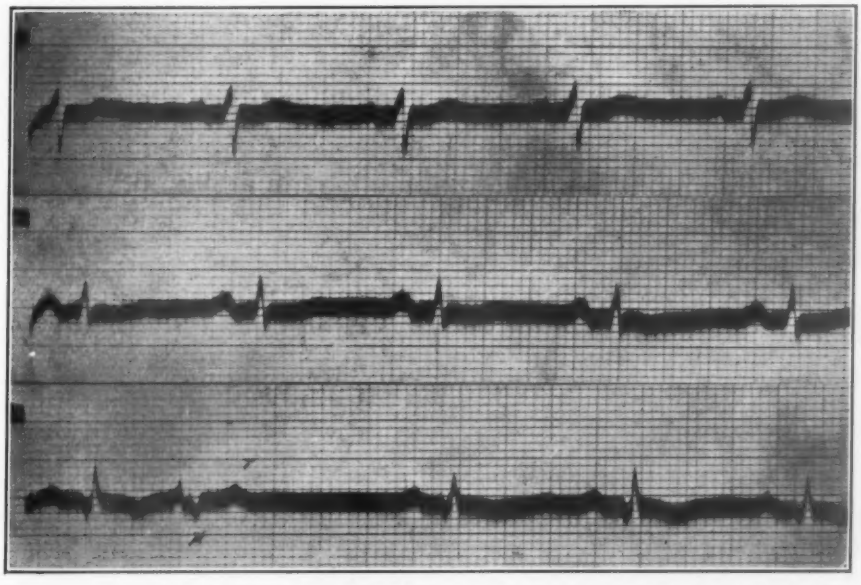

Fig. 1.—Electrocardiogram showed slurring of QRS. complexes, right axis deviation, and one aberrant ventricular complex.

The abdomen was large and flabby, and there were shifting dullness and flaring of the flanks. The liver edge was four fingerbreadths below the costal margin, firm, regular, and tender. There was slight dependent edema extending to the sacrum.

Course and Progress.—He improved greatly on massive doses of urea (69 gm. daily) and salyrgan and lost most of his edema. He continued to bring up bloody sputum occasionally. Despite diuretic therapy, congestive heart failure and ascites recurred, and paracentesis of the abdomen had to be performed repeatedly, with removal of from 2,500 to 3,500 c.c. of a slightly turbid, amber-colored fluid. On Jan. 14, 1931, he suddenly vomited considerable dark brown, sour-smelling fluid containing food particles, and became irrational and incoherent. Examination of the chest at this time showed dullness at both bases, with bronchovesicular breath sounds and coarse râles. He subsequently improved, but on Feb. 7, 1931, he had slight swelling of the submaxillary lymph nodes, a rise in temperature, and a blood count of 20,000 white cells, with 86 per cent polynuclear cells. The next day there were

signs of massive consolidation at the left base, in addition to the hydrothorax, a rise in the temperature to 104° F., a rapid pulse, cyanosis, and a respiratory rate of 32 per minute, attributed to lobar pneumonia. Thoracentesis of the left chest yielded 200 c.c. of serosanguineous fluid. He was put in an oxygen tent but died that evening.

Necropsy.—Only the findings referable to the heart are reported.

Measurements:	Tricuspid ring	13 cm.
	Pulmonic ring	7.5 cm.
	Aortic ring	7 cm.
	Mitral ring	11 cm.
	Left ventricular wall	18 mm.
	Left ventricular wall	3 mm. at apex
	Right ventricular wall	8 mm.

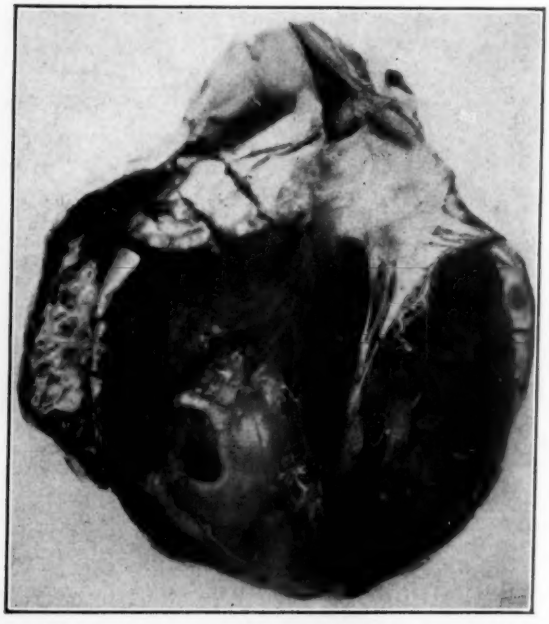

Fig. 2.—Gross picture of heart showing generalized cardiac hypertrophy and marked thinning of apex and replacement fibrosis. Entire lower half of septum shows replacement fibrosis and septal defect in middle of this area.

Pericardial surfaces were smooth and glistening, except for a patch of thickened grayish visceral pericardium over the apex. The heart was uniformly enlarged, and somewhat apple shaped. The right auricle was markedly dilated, and the musculi pectinati were considerably hypertrophied. There was a considerable amount of hypertrophy of the myocardium of the right ventricle and dilatation of the chamber. The tricuspid ring was markedly dilated. The left auricle was considerably dilated, and there was a definite subendocardial fibrosis of the mural endocardium. The mitral valve showed no abnormalities. The left ventricle was slightly hypertrophied and considerably dilated. Papillary muscles were considerably hypertrophied. The apex was thinned out, and the myocardium was replaced by fibrous tissue. The endocardium in this region was thickened and gray. Likewise the entire lower half of the septal wall showed replacement of the myocardium by fibrous tissue with marked narrowing of the endocardium. In the central portion of this area of

fibrosis of the septum was a circular defect, measuring several centimeters in diameter, whose edges were round, regular, and very smooth. This defect when viewed from the right ventricle revealed a large communication between the left and right ventricles. A portion of the right ventricle adjacent to the area of septal fibrosis showed thickened endocardium and small areas of fibrosis. Right coronary artery showed considerable atherosclerosis with calcification and dilatation of the lumen. No areas of narrowing were encountered. The left anterior descending coronary divided into a large deep and a smaller superficial branch about 1 cm. from the origin of the left coronary artery. About 1 cm. from this division a small superficial branch was completely occluded by a yellowish calcific plaque. The deeper branch showed severe atherosclerosis and calcification with frequent narrowing of the lumen by large yellowish gray plaques. The first lateral branch of the left circumflex was completely occluded about 1 cm. from its origin by a reddish firm thrombus. Distally the same artery was completely occluded by a yellowish calcific plaque. Several terminal lateral branches of the left circumflex also showed marked narrowing or complete occlusion by yellowish plaques.

DISCUSSION

The acquired cases of interventricular septal perforation recorded in the literature have chiefly been incidental to coronary artery disease. The course and duration have usually been short, never exceeding ten days. Our case is noteworthy in that, while secondary to severe coronary disease, the defect was healed, large, and smooth, and the patient lived for a long time during which he developed advanced congestive heart failure, which responded to diuretic therapy. It would not be reasonable to conjecture the existence of an independent congenital septal defect with independent coronary disease and myocardial infarction. Both the transverse and descending branches of the left, as well as the right, coronary arteries were markedly involved. The myocardium of the septum up to and including the perforated area was a mass of fibrotic tissue. It is difficult to assume that infarction and fibrosis extended to an area contiguous with a congenital septal defect without sparing an intervening area of normal myocardium between infarcted area and patent septum. The ring around the defect was irregularly sclerotic, the adjacent myocardium extensively scarred, with virtually no remaining muscle tissue left. It is reasonable to assume that an individual with so large a congenital septal defect would not have survived to old age to develop myocardial infarction.

It has been well established that the cases of septal perforation following coronary disease show extensive involvement of both coronary arteries. The richly anastomotic circulation in the septum becomes inadequate so that it is involved as part of the myocardial infarction. Subsequently, with weakening of the wall from alterations in blood pressure, ventricular aneurysm and rupture may occur. Violent effort may be a deciding factor in an already weakened wall in producing perforation.

The diagnosis should offer no great clinical difficulty. In a known case of coronary artery disease, a murmur appearing in the fourth and

fifth left interspaces and over the precordium, as in the common type of interventricular defect, should lead to the correct diagnosis. The presence or absence of a thrill and its intensity depend upon the size of the defect, being louder with smaller ostia. In this case, the presence of a presystolic apical rumble, systolic apical thrill, and marked accentuation of the pulmonic second sound, led to a diagnosis of a rheumatic mitral stenosis. There was, however, a prolonged systolic murmur of unusual intensity over the entire precordium and base, loudest at the ensiform area and apex, as in typical congenital septal defect. It was thought difficult to correlate the location and intensity of the murmur with simple coronary disease. A murmur suggestive of a congenital interventricular septal lesion in a known case of coronary disease justifies labeling the septal defect as an acquired one.

SUMMARY

An additional instance of an acquired interventricular septal defect secondary to coronary disease is reported. The case is noteworthy in that the individual, despite coronary artery and septal disease, lived long enough to develop chronic congestive heart failure, which for a considerable period was amenable to the usual diuretic measures.

REFERENCES

1. Freeman, W., and Griffin, E. D.: Cardiac Rupture With Perforation of the Interventricular Septum, AM. HEART J. 7: 732, 1932.
2. Kepler, E. J., Berkman, J. M., and Barnes, A. R.: Acute Myocardial Infarction With Rupture of the Interventricular Septum, Complicated by Hyperglycemia Without Glycosuria: Report of a Case, Proc. Staff Meet. Mayo Clin. 10: 209, 1935.
3. Sager, R. V.: Coronary Thrombosis: Perforation of the Infarcted Interventricular Septum, Arch. Int. Med. 53: 140, 1934.

Department of Reviews and Abstracts

Selected Abstracts

Robb, Jane Sands, and Robb, Robert Cummings: The Excitatory Process in the Mammalian Ventricle. Am. J. Physiol. **115**: 43, 1936.

Simultaneous direct and indirect leads have been recorded from mammalian hearts on a multigalvanometer set-up in which the three galvanometers were connected through resistance to a central terminal.

A standard Lead II could therefore be accurately compared with any two points on the surface of the heart without introducing error of time or potential of the direct electrodes.

When times of initial negativity are read from tracings obtained by placing the direct electrodes along the axis of given muscle bundles, these times on the superficial sinospiral and superficial bulbospiral muscles are found to increase in an orderly manner from apex tc base.

Data are cited from literature which could also be interpreted as showing progressive delay in activity along the superficial sinospiral muscle.

Conduction rates calculated from point to point along a muscle strand give a mean value of 2375 ± 128 mm. per second.

Conduction rates for the dog and monkey *(Macacus rhesus)* are not statistically distinguishable.

If any two direct contacts along a given muscle band are separated by a cut, there occurs a delay in the arrival of the intrinsic wave at the contact farthest from the apex. If the whole cross-section of the muscle is involved, the intrinsic wave disappears from the contact farthest from the apex.

Evidence is presented that the wave of excitation does cross the interventricular groove.

These observations cannot be explained according to the present theory of conduction of the excitatory process in the ventricle, i.e., the "radial penetration" theory of Lewis.

These data indicate that the excitatory process is conducted "axillary" in the muscles studied along a pathway parallel to fiber direction.

AUTHOR.

Green, Harold D.: The Coronary Blood Flow in Aortic Stenosis, in Aortic Insufficiency and in Arterio-Venous Fistula. Am. J. Physiol. **115**: 94, 1936.

Since circulatory abnormalities such as aortic insufficiency, aortic stenosis and arteriovenous fistula produce striking changes in the heart and circulation and occasionally myocardial injury, knowledge of their effects on coronary circulation has considerable clinical and physiological significance. The effects of these abnormalities on coronary circulation have therefore been studied in the dog by a slight modification of the method previously reported by Green, Gregg, and Wiggers.

These studies revealed that under the conditions of these experiments (1) lesions of the type of uncompensated aortic insufficiency and arteriovenous fistula cause a decrease in coronary flow chiefly during diastole, by lowering aortic diastolic pressure; (2) this decreased flow is, to a considerable extent, mitigated by a concomitant

increase in the coronary flow during systole resulting from a relative lowering of the systolic peripheral coronary resistance in relation to aortic pressure; (3) in these lesions, compensation through peripheral vascular constriction, sufficient to restore a normal mean blood pressure, may increase coronary flow to or even above normal because the systolic peripheral coronary resistance is elevated relatively less than the aortic pressure; and (4) lesions such as aortic stenosis decrease coronary flow mainly during systole by causing a relatively higher degree of systolic peripheral coronary resistance in relation to aortic pressure.

The question is raised whether an increased flow, such as that obtained by compensation during aortic insufficiency, is commensurate with the increased work of the heart.

It is concluded that the increased systolic peripheral coronary resistance in aortic stenosis is caused by the abnormal height of intraventricular systolic pressure compared with aortic systolic pressure. Some of the factors considered in the attempt to explain the other changes of peripheral resistance observed are that the diastolic size of the ventricle and the wide pulse pressure operate in some manner to alter the extravascular constriction of the vessels and that reflex or metabolic action may cause changes in vascular size. It is considered impossible, however, at the present time to arrive at any definite conclusions.

AUTHOR.

Scott, John C.: The Cardiac Output in the Standing Position. Am. J. Physiol. **115**: 268, 1936.

The cardiac output of a single individual has been observed in the recumbent, sitting, and standing positions. During the winter season in the standing position high A-V differences are usually associated with high oxygen consumption; in the summer this relationship is reversed. The average standing cardiac output is lower than that of the recumbent or sitting positions. The output is influenced by various undefined environmental factors under so-called basal conditions, particularly if the subject is standing.

AUTHOR.

Read, J. Marion, and Barnett, Charles W.: New Formulas for Predicting Basal Metabolic Rate from Pulse Rate and Pulse Pressure. Arch. Int. Med. **57**: 521, 1936.

A new method for the derivation of formulas for predicting the basal metabolic rate from pulse rate and pulse pressure is reported.

The accuracy of the new formulas is compared with that of certain former ones.

The inaccuracy of the determination of basal metabolism by indirect calorimetry is pointed out.

The accuracy of the new formulas is shown to compare favorably with the accuracy of clinical calorimetry.

These formulas are valuable (1) for estimating the basal metabolic rate if the facilities for measuring the consumption of oxygen are not available and (2) for checking the reliability of the metabolic rate as determined by indirect calorimetry. If there is a marked disparity between the results obtained by the two methods, the test should be repeated. In many cases the metabolic rate predicted by the pulse rate and pulse pressure obtained in the morning before the patient arises may be more accurate than the rate determined by measuring the consumption of oxygen after the patient has arisen, dressed, and traveled to a laboratory.

AUTHOR.

Orgain, Edward S., Wolff, Louis, and White, Paul D.: Uncomplicated Auricular Fibrillation and Auricular Flutter: Frequent Occurrence and Good Prognosis in Patients Without Other Evidence of Cardiac Disease. Arch. Int. Med. 57: 493, 1936.

Paroxysms of auricular fibrillation and of auricular flutter occur not infrequently in persons with no other signs of cardiac disease.

Follow-up studies on 54 patients of the present series (47 with auricular fibrillation alone, 5 with auricular flutter alone, and 2 with both) revealed, after the lapse of a significant number of years, a low mortality rate, little important cardiac disease, and but a single instance of hyperthyroidism.

The prognosis for life and for the maintenance of adequate cardiac function is good.

The outlook for future improvement, manifested by a decrease in frequency or complete cessation of paroxysms, is frequently good.

Thus, auricular fibrillation and auricular flutter are in some persons merely exaggerated functional disorders of the heart, no more indicative of cardiac disease or of a poor prognosis than are premature beats or auricular paroxysmal tachycardia.

AUTHOR.

Holzer, W.: The Transmission of Electric Currents Through Biological Material—Including Comments on the Electrocardiographic Method. Ztschr. f. Kreislaufforsch. 28: 113, 1936.

The author develops the theory of recording electrical currents mathematically, taking into account the properties of the biological material containing the current generator, the skin resistance and capacity, and the resistance of the measuring instrument, as well as the vibration frequency of the generated current. Twenty-four determinations on five individuals with Lead II, using silver electrodes, gave a calculated value for the internal resistance of 740 ohms on the average, and a range of 600 to 1,000 ohms. The skin resistance was 2,000 to 16,000 ohms/cm.^{2} (average 8,400 ohms/cm.^{2}); skin capacity was 0.01 to 4 microfarads/cm.^{2} (average 0.36 microfarads). A harmonic analysis of a normal electrocardiogram obtained from averaging 42 curves (Lead II) was made. No vibrations over 200 were present. The author advocates the use of a "direct voltage" amplifier and a cathode ray oscillograph for electrocardiographic registration. The curves so obtained showed the presence of an S-wave and splintering of the R-wave.

L. N. K.

Frey, Leopold: The Relationship Between "Variable Bundle-Branch Block" and Extrasystoles in Malignant Diphtheria. Ztschr. f. Kreislaufforsch. 28: 73, 1936.

The author reports two cases in which the electrocardiogram showed complete A-V block, arborization block, and "variable bundle-branch block." The contour of the ventricular extrasystoles which appeared resembled the ventricular complexes of some of the idioventricular beats. The author concludes from this that the two types of beats arose from the same focus.

L. N. K.

Danzer, C. S.: The Diagnostic Significance of Gallop Rhythm. New York State J. Med. 36: 10, 1936.

It is pointed out that gallop rhythm generally occurs as a sign of serious myocardial disease of impending or obvious heart failure. Gallop rhythm is probably the most direct sign of heart failure, and perhaps of myocardial disease, especially

when this phenomenon is associated with an increase in the P-R interval or an inversion of the T-waves in the two leads of the electrocardiogram.

Gallop rhythm also occurs occasionally in compensated aortic insufficiency, severe tachycardia, Graves' disease, and with auricular extrasystoles without concurrent heart failure.

PART OF A SYMPOSIUM
on
RHEUMATIC FEVER
at the
Second Annual Meeting of The American Association for the Study and Control of Rheumatic Diseases and the Fourth Conference on Rheumatic Diseases
June 10, 1935
Atlantic City, N. J.

Swift, Homer F.: The Nature of Rheumatic Fever. J. Lab. & Clin. Med. **21**: 551, 1936.

Rheumatic fever presents protean manifestations, which, when few in number, often make it difficult to distinguish the disease from closely related conditions; hence it is impossible to characterize the malady too accurately. The histopathological picture, while presenting the well-recognized manifestations of inflammation, has certain peculiar features, chief of which are damage to the mesenchymal ground substance by some noxious agent, the nature of which has not been definitely established; this damage is followed by hyperplasia and multiplication of primitive cells that often assume a definite architectural form. Inflammatory features are seen early in the rheumatic lesion in contrast to the initial cellular injury followed by the signs of inflammation usually seen in virus-induced diseases. The tissue of rheumatic patients appears to be unusually vulnerable to several injurious agents, and especially to substances contained in or derived from streptococci. Possibly this state of hypervulnerability, or allergic irritability, makes the tissues susceptible to the action of a hypothetical specific virus; on the other hand, the state of allergic irritability may be the result of prolonged action of such a virus, and the immediate attack may be merely set off by a bacterial infection or other traumatic insult. While much investigation remains to establish firmly and to correlate many of the phenomena discussed, the following working hypothesis remains to guide prophylaxis: It appears advisable to protect the rheumatic subject from certain bacterial infections as well as from other injurious and depressing influences if he is to be spared the repeated attacks of a disease that eventually lead to permanent cardiac disability, for repeated or recurring infections usually exert a more deleterious influence than does the initial attack.

AUTHOR.

Shapiro, M. J.: The Natural History of Childhood Rheumatism in Minnesota. J. Lab. & Clin. Med. **21**: 564, 1936.

Rheumatic disease in children in Minneapolis is essentially the same as in other centers throughout the world.

Rheumatic fever is more prevalent in Minneapolis in the early spring and late fall. During the summer the disease is at its lowest ebb. Similar curves from other large centers are presented.

Childhood rheumatism occurs most commonly in children between five and six years of age.

This disease is definitely familial. The familial tendency is three times as great in a rheumatic group as in a nonrheumatic group.

Rheumatism in children in a considerable number of instances follows an upper respiratory infection, but most commonly develops slowly with no preceding infectious process.

The great majority of children who complain of leg pains are not suffering from rheumatism. A differential diagnostic table based on clinical observations is presented.

The normal expectancy of recurrences of rheumatism has been determined. This material is to be used as a control in determining the efficacy of any type of specific treatment which might be tried in the future.

An analysis of the findings of thirty-four children who have died is presented.

AUTHOR.

Dawson, M. H., and Tyson, T. Lloyd: The Relationship Between Rheumatic Fever and Rheumatoid Arthritis. J. Lab. & Clin. Med. **21**: 575, 1936.

The relationship between rheumatic fever and rheumatoid arthritis is, at the present time, of greater theoretical than practical importance. For clinical purposes it is important that the two should be differentiated whenever possible for, in typical cases, each presents its own symptoms, each demands its own therapeutic management, and each requires its own prognosis. For theoretical reasons, however, a clearer understanding of the nature of the relationship of the two diseases is of great importance and may contribute much to our knowledge of both conditions.

Evidence has been presented to show that rheumatic fever and rheumatoid arthritis are intimately related and possible different manifestations of the same pathological process. Of particular significance is the clinical and anatomical evidence obtained from a study of "atypical" and "borderline" cases. The clinical evidence suggests that the two form a continuous sequence of one disease process with different expressions in each individual phase. These different expressions appear to be in large measure determined by the age of the patient, but undoubtedly other factors, such as individual host susceptibility, are also of importance. The pathological evidence, representing a difference in degree rather than in kind, strongly suggests that the two represent different responses to the same, or closely related, etiological agents.

A final understanding of the relationship between rheumatic fever and rheumatoid arthritis will not be possible until the etiology of both diseases has been definitely established. At the present time there is a certain amount of evidence suggesting that infection by *Streptococcus hemolyticus* plays a rôle in the production of both diseases. However, this evidence is as yet far from complete, and, even if it could be established that both diseases were due to the same agent, it would not prove their identity. The situation would then be analogous to that which exists with syphilis and yaws. Here the etiology of both diseases is definitely known, yet the relationship between the two is still a matter of controversy. It is obviously more difficult, with the knowledge at present available, to arrive at a complete understanding of the relationship between rheumatic fever and rheumatoid arthritis.

AUTHOR.

Nichol, E. Sterling: Geographic Distribution of Rheumatic Fever and Rheumatic Heart Disease in the United States. J. Lab. & Clin. Med. **21**: 588, 1936.

A review of available data indicates that there is a definite inequality in the distribution of rheumatic fever and rheumatic heart disease in the United States, the amount being much less in the southern states. The influence of geographical location on the clinical incidence of rheumatic fever and rheumatic heart disease is emphasized by contrasting the findings in southern Florida and New England. During the past five years, in spite of a careful search for subclinical cases, the admission

rate of rheumatic fever, rheumatic carditis, or chorea in a general hospital in Miami was only one-tenth the rate in Boston during the same period.

Only 1.3 per cent of "cardiac" patients found in Miami both in hospital and office practice had rheumatic heart disease determined clinically to have been acquired during life or residence in the South, as compared with a recent estimate that 31.9 per cent of "cardiac" patients encountered in New England were of rheumatic type. AUTHOR.

Rinehart, James F.: An Outline of Studies Relating to Vitamin C Deficiency in Rheumatic Fever. J. Lab. & Clin. Med. **21**: 597, 1936.

The concept that rheumatic fever may be due to the combined influence of vitamin C deficiency and infection rests upon a broad experimental basis. In guinea pigs, under this dual influence, lesions comparable to those of rheumatic fever may develop in the heart and joints. The not infrequent occurrence of subcutaneous nodules appears to complete the pathological similarity. It is of interest that in the experimental work no sharp line can be drawn between a disease picture resembling rheumatic fever and one characterized by a chronic joint disability with pathological similarities to atrophic (rheumatoid) arthritis. There is much evidence indicating a relationship between the two diseases as seen in man.

Epidemiological data seem to support the thesis advanced. Particular significance is attached to the abnormally high incidence of rheumatic fever in the poor.

Clinical studies in progress have afforded encouraging data but are too few, and the period of observation is too short to afford a basis for judgment.

Rheumatic fever is a disease fundamentally characterized by widespread injury to collagen. Based upon the experimental studies and pathologic anatomy of rheumatic fever, a theory of mechanism of the development of the rheumatic lesion is advanced.

Our knowledge of the metabolism of vitamin C is in the process of development. Capacity to store the vitamin is limited. Fatigue and certain infections may deplete the organic reserve. Factors which might inhibit absorption or utilization of vitamin C are not known. Urinary excretion studies may serve as an index of the immediate "saturation" level but are not a gauge of preexisting deficiency. The possible influence of infection in modifying the storage and excretion or utilization of vitamin C is not known. For these reasons, data based upon urinary excretion must be interpreted with care.

The question of what we may reasonably expect from vitamin C therapy in rheumatic fever is considered in the light of the fundamental pathology of the disease. Even though vitamin C deficiency may contribute to the development of the rheumatic lesion, it is only one factor. Some influence of infection also operates. In view of this and the frequently severe injury accompanying the disease, judgment of the preventive or therapeutic effectiveness of vitamin C administration in rheumatic fever can be based only on prolonged clinical study.

AUTHOR.

Sutton, Lucy Porter, and Dodge, Katharine G.: Fever Therapy in Chorea and in Rheumatic Carditis With and Without Chorea. J. Lab. & Clin. Med. **21**: 619, 1936.

Fever, by whatever means produced, is a satisfactory method of treatment of chorea, in that the duration of the attacks is thereby appreciably shortened.

The presence of subacute carditis or of inactive rheumatic heart disease is not a contraindication to the use of fever therapy in treating chorea.

The subsequent uphill course of patients with subacute rheumatic carditis who received fever therapy suggests that fever may be of benefit to such patients. We believe that further investigation is warranted. AUTHOR.

Schmitt, H.: Experimental Investigation of "Rheumatic Atherosclerosis" (Lipoid Deposits in the Vessel Walls After Allergic Injury). Virchows Arch. f. path. Anat. **296**: 603, 1936.

The author succeeded in producing marked atherosclerotic changes in rabbits which previously were made sensitive to hog serum by feeding 4.4 grams of cholesterol over a period of two weeks. Nonsensitized rabbits were found to require two to four months and many times as large a dose of cholesterol to cause atherosclerosis. The changes found anatomically were atherosclerosis of the aorta with lipoid deposits and calcification. In one of these cases marked proliferation of the intima with occlusion of the lumen of one of the coronary arteries was found.

A group of rabbits which received the cholesterol at the time they were sensitized to hog serum showed a combination of inflammatory and degenerative changes of the vessel walls (adventitia, media, and intima) and marked atherosclerotic changes.

The author believes that early atherosclerosis, particularly in young subjects and especially in the coronary arteries, probably is the result of previous toxic-inflammatory damage to the vessel walls.

A. V.

Root, Howard F., and Sharkey, Thomas P.: Arteriosclerosis and Hypertension in Diabetes. Ann. Int. Med. **9**: 873, 1936.

The clinical and post-mortem records of 175 diabetic patients were examined. Fifty-four per cent of the patients had had hypertension, indicated by a systolic pressure exceeding 150 mm. of mercury. Eighty-seven per cent of the patients with hypertension and 74 per cent of the patients without hypertension were obese. Arteriosclerotic lesions were found much more frequently in this group of patients than in a similar group of patients without diabetes. If, however, the diabetes was of short duration, severe arteriosclerosis in the aorta occurred somewhat less than in nondiabetic patients, but if the duration of the diabetes exceeded ten years, coronary disease as a cause of death was four times as frequent in the diabetic as in the nondiabetic control series. When accurate data were available, it was found that in the majority of instances diabetes preceded the appearance of hypertension, which affects diabetic patients much more frequently than nondiabetic patients. Gangrene of an extremity had affected 48 of the 175 diabetic patients. Of this group 32 had had hypertension.

Pathologically, the difference in the arteries of patients with and without diabetes who have had gangrene consists in a marked localized proliferation of the intima with deposition of the fatty material including cholestrol crystals in the arteries of diabetic patients.

The authors believe that the premature and excessive development of vascular disease occurs predominantly in muscular arteries under the physical strain, especially in obese patients, and is due to the metabolic changes of diabetes. Hypertension is an important contributing factor in the clinical course of diabetes because it imposes additional strain, even when the patient has lost his obesity, and accentuates greatly the vascular changes in coronary and leg arteries.

E. A.

Clares, Fernando Lopez: Arterial Pressure in Mexican Children. Arch. latino am. de cardiol. y hemat. **5**: 235, 1935.

Children's blood pressure was taken with the kymometer of Baquez, Gley, and Gomez, using also the oscillatory method from birth up to the age of four months and a combined oscillatory and auscultatory method from the age of four months up to fourteen years; averages for the systolic and diastolic pressures were taken

with the auscultatory method, and averages for the medium pressure with the oscillatory method, taking into consideration the differences between the methods and using cuffs of the following sizes: 4.5 by 14.5 cm., 6 by 19 cm., 1 by 28.5 cm., and the one used on adults, putting the cuff on the left arm.

During the first fifteen days the blood pressure has alternatives increasing and decreasing in both sexes, beginning with the following pressures: newborn infants, systolic 70, medium 60, diastolic 50. The average on the sixteenth day, systolic 77, medium 65, and diastolic 55 in boys, and systolic 75, medium 63, and diastolic 50 in girls. It was noted that blood pressure increases rapidly during the first twelve months in close relation to body strain and weight, being the physiological constant of systolic 85, medium 68, and diastolic 55 in boys and systolic 82, medium 68, and diastolic 51 in girls.

During puberty the blood pressure is higher in girls from twelve to fourteen years old than it is in boys. The blood pressure is lower in premature infants than in those born at term. During the course of the infections and nutritional diseases it is always a dangerous sign when the blood pressure shows a marked and sustained decrease.

Hypertension is very seldom found in children without the clinical manifestations, but nevertheless records should be determined.

H. McC.

Lindenbaum, I., and Kapitza, L.: The Clinical Picture and Pathological Histology of Buerger's Form of Thrombo-Angiitis Obliterans. Arch. f. klin. Chir. **184**: 413, 1936.

The authors report a series of 22 cases. They emphasize particularly the phlebitis which accompanies the arterial manifestations of the disease and divide the cases into three stages consisting of (a) migrating phlebitis with little or no arterial symptoms, (b) migrating phlebitis with definite arterial symptoms, and (c) migrating phlebitis accompanied by arterial thrombosis. They advise sympathectomy for patients in the second stage and for those in the first with beginning arterial manifestations. Segments of inflamed superficial veins were removed for biopsy in sixteen patients. The clinical and histological pictures support the allergic theory as to the origin of the disease.

L. M. Z.

Fonia, A., and Vanotti, A.: New Experiments on the Origin of Thrombosis. Schweiz. med. Wchnschr. **64**: 1086, 1934.

Experimental venous thrombosis produced in frogs' tongues was observed with the help of a capillary microscope. On coagulating the endothelial wall of a vessel with a platinum micro-electrothermocautery, spindle-shaped cells, which are the equivalent of human thrombocytes, accumulated at the place of the injury and covered it. This concentration of such cells continues over the injured wall until it entirely obliterates the vessel. The lowered rate of blood flow accelerates this procedure. Lowered rate of blood flow without injury of the epithelium does not produce thrombosis.

J. K.

Kraus, Herbert: Effect of Intravenous Injection of Different Iodine Preparations on the Peripheral Vessels. Naunyn-Schmiedbergs Arch. **179**: 537, 1935.

Intra-arterial injection of drugs containing iodine, such as abrodil, uroselectan, and tenebryl, increased the peripheral circulation, due to dilation of the peripheral vessels. In experiments on rabbits and dogs, the peripheral vessels showed dilation after intravenous injection of such drugs, while in cold-blooded specimens the re-

action was absent. When pituitrin or adrenalin was administered previously, larger doses of these iodine preparations failed to produce vasodilation. The time of vasodilation was short, lasting only as long as the preparation remained adequately concentrated in the blood stream.

J. K.

Huggins, C. B., Blockson, B. H., and Wilson, Harwell: Thermal Changes in Local Asphyxia and Reactive Hyperemias. Arch. Surg. **32**: 528, 1936.

Complete mechanical obstruction to the flow of arterial blood in man resulted in a gradual fall in temperature of the skin below the area of constriction and a slow but steady rise of the temperature in the control limb and above the tourniquet in the experimental limb. At the time of release there was a large increase in temperature above the initial readings in the limb to which the constriction had been applied and a sharp fall in the temperature of the skin of the control limb. A similar type of experiment on rabbits showed that the temperatures in the bone marrow and the muscles of the limb react similarly to that of the skin of man as a result of mechanical constriction. Partial asphyxia of the limb produced by distention of the constricting cuff to the diastolic blood pressure caused gradual diminution in the temperature of the skin of the extremity, which diminution continued after the tourniquet was removed. The injection of adrenalin into the femoral artery of dogs immediately after the removal of the tourniquet, which had produced complete asphyxia, prevented the hyperthermia which ordinarily follows the removal of the tourniquet. The injection of adrenalin directly into the femoral artery of dogs caused a gradual diminution of the temperature of the skin, which returned to normal in about two hours. Injection of adrenalin into the femoral artery of men caused a rise in the systemic blood pressure, tachycardia, and dyspnea. The experimental leg became cadaveric in appearance, and there was complete obliteration of the pulses in the dorsalis pedis and posterior tibial arteries. The temperature of the skin lessened. Recovery began in about twenty-five minutes after injection. Subcutaneous injection of adrenalin in the region of a subcutaneous thermocouple produced a marked fall in the temperature.

E. A.

Marcovich, P.: Peripheral Thermooscillometry. Cuore **19**: No. 5, 1935.

The leg with oscillometer attached was immersed for five minutes in cold water at 7° C. and later for five minutes in warm water at 42° C. In normal conditions heat produced an increase, and cold caused a decrease in the oscillometric readings. Amyl nitrite had the same effect as heat on the oscillometric readings, but the reaction following administration of acetylcholine was so small that no definite conclusions could be made.

J. K.

Hustin, A.: Vasmotor Reactions in Men in Normal and Pathological Conditions. Lyon Chir. **32**: 384, 1935.

On compressing one arm, the skin temperature of that member was lowered, but it quickly returned to normal upon relieving the compression. At the same time a brief temperature drop was observed in the other arm. It seems that compression prevents a contralateral vasoconstricting reflex which would be activated by the cooling of the compressed arm. Mental excitement lowered the skin temperature, while the rectal temperature remained unchanged. Immersion of one arm in cold water caused the skin temperature of the other arm to drop, because of a contralateral reflex. The temperature drop could be prevented by compressing the cooled arm.

Temperature studies during narcosis showed the following vasomotor changes: (1) vasoconstriction at the beginning stage, due to excitement; (2) vasodilation due to paralysis of the nerve center (in spinal anesthesia through interruption of the afferent reflexes); (3) constriction on return to consciousness; and (4) dilation. For three to four days following narcosis, the usual fluctations in the skin temperature were absent.

Lumbar sympathectomy increases the skin temperature of the lower extremities, and their temperature approaches the rectal temperature. Sympathectomy seems to reduce the sensitiveness of the arteries to internal and external impulses. The same results are seen after periarterial sympathectomy—constant dilation of the vessels.

J. K.

Watson, Charles M., and James R: Autotransfusion in the Treatment of Wounds of the Heart, J. A. M. A. **106:** 520, 1936.

Autotransfusion was used to combat the excessive loss of blood resulting from a stab wound of the heart. The blood was obtained from the pleural cavity during the operation, was filtered through gauze, and was injected intravenously.

As far as can be determined by a review of the literature, this is the first time autotransfusion has been used in the treatment of this type of injury. In view of its marked success in this instance, the authors believe that it should receive further trial as an adjunct to cardiorrhaphy in those cases in which the loss of blood is sufficient to threaten the immediate survival of the patient.

H. McC.

Sanders, C. E.: Cardiovascular and Peripheral Vascular Diseases: Treatment by a Motorized Oscillating Bed. J. A. M. A. **106:** 916, 1936.

The bed described is equipped with motor and tilting device which alternately elevates and lowers the head and the foot. The starting and stopping and speed of the tilting are under control of the patient or attendant.

Its advantage is claimed to lie in the changing distribution of body weight it accomplishes, and in the use of gravity in altering the mechanical factors influencing impaired circulation, whether of cardiac or peripheral vascular origin.

L. H. H.

di Cio, Alfredo V.: Carbondioxide and Carbogen in the Therapy of Peripheral Arterial Diseases. Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch. **8:** 201, 1935.

Filtrated gas was injected intradermally in the thigh. The beginning dosage, 250 c.c., was increased daily, according to the tolerance of the patient, to a maximum of 600 to 700 c.c. Absorption took place in from twelve to sixty hours. The best results were obtained with a mixture consisting of 95 per cent oxygen and 5 per cent carbon dioxide. There seemed to be objective and subjective improvement in cases of acrocyanosis and endarteritis obliterans.

J. K.